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The Bancroft Memorial Lecture.[1]

THE CLINICAL SIGNIFICANCE OF RESEARCH WORK ON THE CHEMICAL TRANSMITTER SUBSTANCES OF THE NERVOUS SYSTEM.

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IT is a great privilege to be giving an oration in memory of that notable Australian scientist Joseph Bancroft. Since my field of research is so different from his, it is not possible for me to choose a topic related to his pioneer research work. However, I thought that it would be appropriate to give you an account of research which likewise has largely been carried out in Australia, and which has certainly great potential importance in clinical medicine. I therefore am going to give an account of investigations relating to transmission across neuro-muscular junctions and synapses in the central nervous system. I hope that I shall be able to show you that this work is of significance in clinical neurology and gives great promise for the future.

[1] Delivered at a meeting of the Queensland Branch of the British Medical Association on August 24, 1956.

Let me deal firstly with the simplest situations at which transmission occurs from one cell to another. At the neuro-muscular junction the nerve fibre ends as complex branches closely applied to the surface of the muscle fibre. There is believed to be a space between the nerve ending and the muscle surface, and furthermore we know that, when a nerve impulse reaches the ending, it causes the emission of a jet of acetylcholine, which acts on the surface of the muscle fibre, removing a considerable amount of the charge thereon (Castillo and Katz, 1956). Very recently extremely high magnification by electron microscopy (Figure I) has shown that the nerve ending is indeed separate from the muscle, and that the cleft between them (about $^1/_{20}\mu$) is even narrower than we had imagined (Robertson, 1956). Furthermore, it shows that there are very fine vesicles in the nerve terminals. Recent work with intracellular recording (Figure I), first in England (Fatt and Katz, 1952) and then in Canberra (Liley, 1956*a*), has indicated that these vesicles are being discharged all the time into the cleft and so onto the muscle, giving small quantal depolarizations as in Figure II, A, which have been called miniature endplate potentials, and which occur at a rate of a few per second at a normal ending. A nerve impulse causes approximately 100 of these vesicles to burst on the surface in the course of a few microseconds; that is, the rate is increased millions of times. Liley (1956*c*) has shown that the depolarization produced by the nerve impulse can account quantitatively for this enormous increase. However, when neuro-muscular transmission is

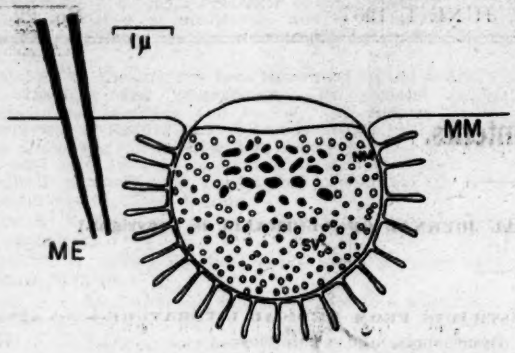

FIGURE I.

Diagrammatic representation of electron-microscopic picture of nerve terminal lying in a groove on the muscle surface. It is bounded by the nerve membrane, NM, and filled with mitochondria and synaptic vesicles, SV. The surface membrane of the muscle, MM, is seen to be deeply folded at the region of the junction, and nearby is penetrated by a microelectrode which is placed for effective recording of miniature endplate potentials (modified from Robertson, 1956.)

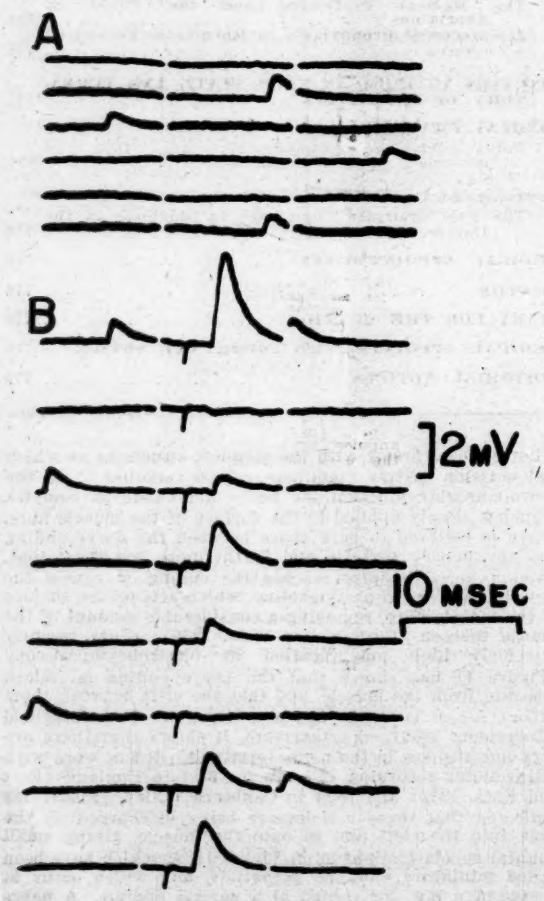

FIGURE II.

Intracellular recordings in an isolated rat diaphragm of fluctuations in endplate potential response at junctions treated with Ca 1 mM, Mg 6 mM. A: Spontaneous miniature potentials. B (same fibre as A): Endplate potential responses. Note scattered spontaneous miniature potentials on records; also intermittent failure of response (Liley, 1956b).

greatly depressed by magnesium, a nerve impulse causes the release of very few quanta of acetylcholine (Figure II, B). It is very interesting to have, in this way, the possibilities of correlation between the latest work in electron microscopy and the highly sensitive recording of events at the surface of the muscle fibre (Castillo and Katz, 1956).

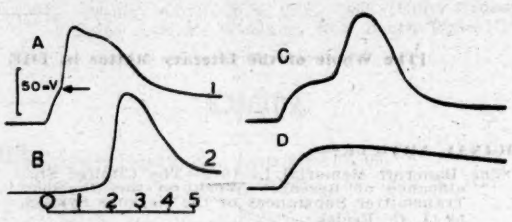

FIGURE III.

Intracellular potentials of a muscle fibre evoked by a single nerve impulse and recorded A at the endplate region as in Figure I, and B, 2·5 millimetres away. In A the arrow marks the origin of the muscle spike potential from the endplate potential. In B the endplate potential is negligible and the spike is seen to be much later (Fatt and Katz, 1952). C and D show diagrammatically the effect of progressive curarization, the spike arising later from the smaller endplate potential in C, while D is just an endplate potential.

If the depolarization of the endplate membrane and hence of the muscle surface membrane is sufficient, it will generate an impulse, as at the arrow in Figure III, A, which travels along the muscle fibre (as in Figure III, B), and so

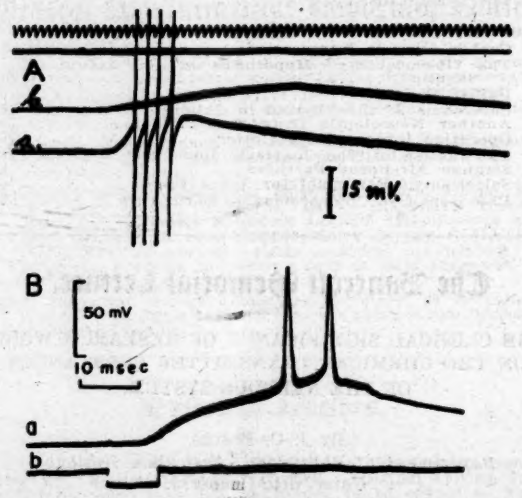

FIGURE IV.

A: Potentials recorded at site of application of acetylcholine to the endplate of a single nerve-muscle fibre. In Aa 10^{-6} acetylcholine caused a sharp depolarization leading on to four impulses, while in Ab a lower concentration gave only a prolonged depolarization (Kuffler, 1943). B: An acetylcholine-filled micropipette was placed on outside of an endplate and a brief outward-directed current pulse through the pipette (trace b) produced the jet of acetylcholine that gave the response of the upper trace as recorded by an electrode placed as in Figure I (Castillo and Katz, 1956).

causes it to contract. Thus we have a sequence of events every time a nerve impulse makes a muscle contract. There is, firstly, the liberation of the jet of acetylcholine from the nerve terminal, then the diffusion of acetylcholine to the specialized endplate surface of the muscle and its attachment thereto. This in turn leads to depolarization

of the muscle membrane, which we call an endplate potential. Finally, if this depolarization is large enough, there is the generation of the muscle impulse. Thus in the transmission from nerve impulse to muscle impulse,

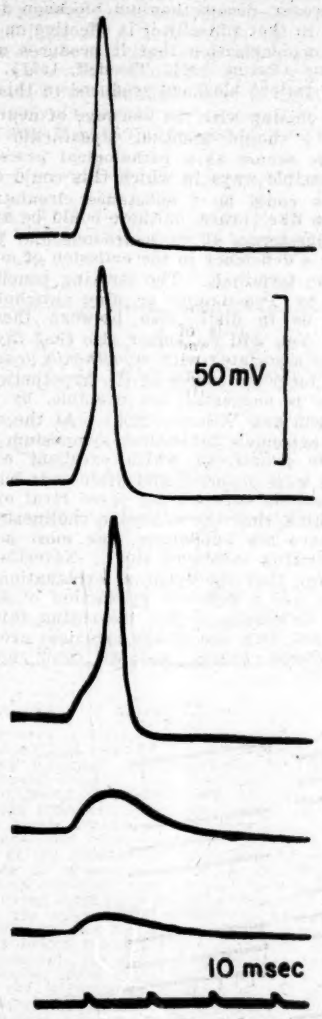

FIGURE V.

Intracellular records from ganglion cells of the isolated superior cervical ganglion in response to a maximal single preganglionic volley. The uppermost record is before and the series below at intervals of several minutes after the addition of a curarizing agent to the bathing solution. Note progressively later origin of the spike potential from the synaptic potential and its eventual failure in the two lower records. Resting membrane potential unaltered (R. M. Eccles, 1956).

acetylcholine plays the vital role of a chemical transmitter, bridging the gap between these two structures. In Figure III, C and D, we can see that this role of the endplate potential in setting up a muscle impulse can be antagonized by curare, so that the generation of the muscle impulse is progressively delayed and eventually fails; that is, curare has paralysed the neuro-muscular junction. Moreover, it is believed to do this by its power of adhering to those parts of the surface membrane to which normally the acetylcholine molecules become attached, and in that way it depresses the size of the endplate potential below the level at which it generates a muscle impulse.

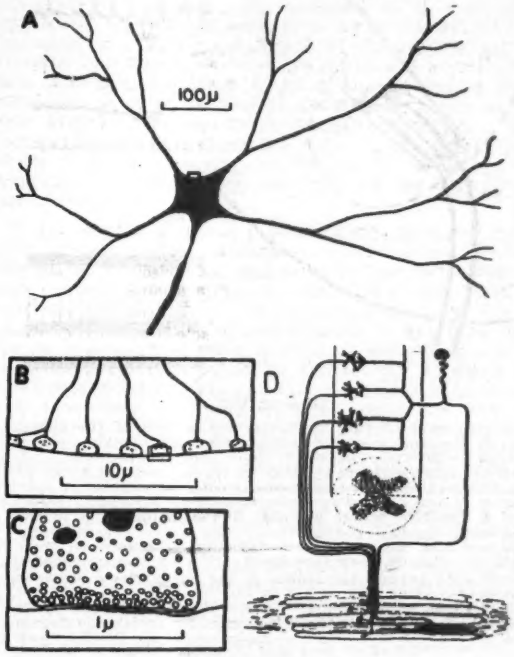

FIGURE VI.

Drawing of a motoneuron to illustrate general relationships of dendrites and axon to the soma. The small surface area that is outlined is drawn at 20 times higher magnification in B to illustrate the relationship of the synaptic knobs to the surface. The small area outlined in B is drawn at ten times further magnification in C to show the width of the synaptic cleft and the thickness of the surface membranes of the synaptic knob and the nerve cell. Also shown are the synaptic vesicles and mitochondria of the synaptic knob. D: Diagram showing reflex pathway for monosynaptic reflex arc with afferent fibre from an annulospiral ending in the muscle to which the reflex discharge returns.

One of the important experiments that indicated the role of acetylcholine is illustrated in Figure IV, A, in which Kuffler (1943) showed that the application of a dilute solution of acetylcholine to the outside of a muscle endplate caused a depolarization, which, when sufficiently large, generated muscle impulses. It was found that curare antagonized these actions of artificially applied acetylcholine just as it does the acetylcholine liberated from the nerve terminal in Figure III, C and D. In Figure IV, B, we see the application of acetylcholine to a neuro-muscular junction by a more refined technique (Castillo and Kats, 1956) which resembles ionophoresis, and by which minute amounts can be applied in a few thousandths of a second. The effect is greatly prolonged by "Prostigmin", an action which is attributable to its suppression of the activity of cholinesterase, the enzyme that destroys acetylcholine.

Until about fifteen years ago, the work on curare had been pursued purely because of its physiological and pharmacological interest. As you know, its action in paralysing animals was first discovered by the South American Indians; but it was not until 1942 that Griffith, of Montreal, thought of applying this action to produce muscle relaxation during operations. This clinical application has been of great value, and now we have a whole host of substances being synthesized in the attempt to discover substitutes for curare which produce a safer and steadier muscle relaxation. I can mention such substances

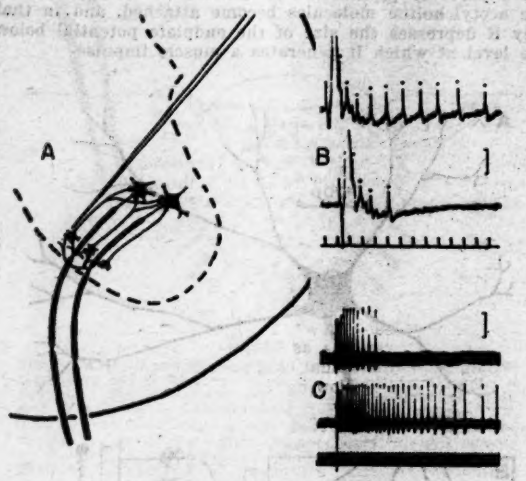

FIGURE VII.

A: Drawing of part of transverse section of the spinal cord, showing proposed nerve pathways involving motor axon collaterals, Renshaw cells and motoneurons. A microelectrode is drawn with its tip in close apposition to a Renshaw cell, as would be the case for recordings such as in B and C. B: Repetitive responses (marked by dots) of a Renshaw cell to a volley in the motor axons of the seventh lumbar ventral root, the upper record being before and the lower after injection of a blocking substance (dihydro-β-erythroidine). The rhythmic response continued beyond ten spikes in the upper series, whereas it ceased after four spikes in the lower. C: As in B, but at a much slower speed, to show in the lower record the effect of an intravenous injection of an anticholinesterase in prolonging the repetitive discharge of the Renshaw cell (Eccles, Fatt and Koketsu, 1954).

cedure, and that is the relief of blockage by "Prostigmin" or other substances which antagonize cholinesterase. You will readily appreciate that any substances which depress the rate of destruction of acetylcholine will tend to counteract the agents which block its action at the neuro-muscular junction. However, decamethonium blockage differs from that of curare in that initially it is effective on account of the enduring depolarization that it produces at the end-plate membrane (Paton, 1951; Thesleff, 1955). "Prostigmin" does not relieve blockage produced in this way.

While I am dealing with the blockage of neuro-muscular transmission, I should mention *myasthenia gravis*, in which blockage occurs as a pathological process. There are several possible ways in which this could occur. For example, there could be a substance circulating in the blood that acts like curare, or there could be an excessive action of cholinesterase at the neuro-muscular junction, or there could be a deficiency in the emission of acetylcholine from the nerve terminals. The striking beneficial effects of medication by "Prostigmin" or other anticholinesterases do not help us to distinguish between these possible explanations. You will remember also that thymic hypertrophy is often associated with *myasthenia gravis*, and the thymus could form the source of the hypothetical blocking substances, as is suggested, for example, by the experiments of Wilson and Wilson (1955). At the end of 1954 there was an extremely interesting symposium in America on *myasthenia gravis*, in which excellent experimental investigations were reported and discussed; but as yet no decision is possible between the three rival explanations. However, I think that the excessive cholinesterase action would now have few supporters, and most people would favour the blocking substance story. Nevertheless, I cannot help feeling that the eventual explanation could still be that there was a deficient production of acetylcholine in the nerve terminals. I was discussing this matter in America in 1955 with one of the principal groups investigating *myasthenia gravis*, and we could not think of

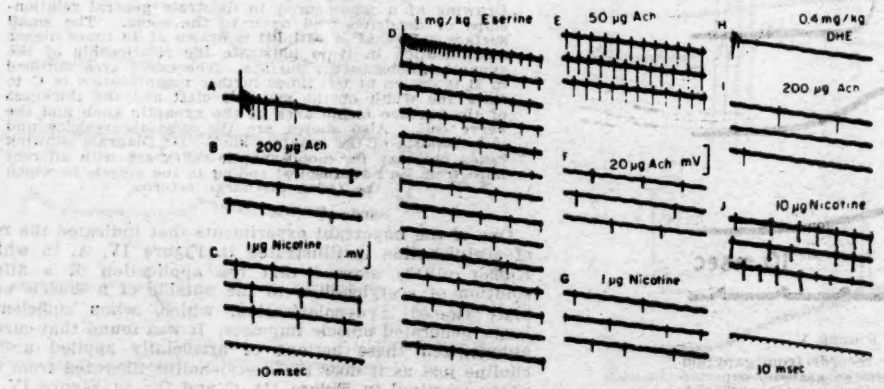

FIGURE VIII.

Responses of another Renshaw cell. There was no spontaneous discharge. A is response to a single antidromic volley in the seventh lumbar ventral root, while B and C each show three successive sweeps at the height of the responses evoked by intraarterial injection of 200 microgrammes of acetylcholine and one microgramme of nicotine, respectively. Several minutes after the intravenous injection of 1·0 milligramme of eserine per kilogram, the response A was changed to D, while E, F and G show, respectively, three successive records at the heights of the responses evoked by the intra-arterial injections of 50 microgrammes of acetylcholine, 20 microgrammes of acetylcholine and one microgramme of nicotine. Records H, I and J were obtained during the maximum of the depression produced by the intravenous injection of 0·4 milligramme of dihydro-β-erythroidine hydrobromide per kilogram, H being evoked by the antidromic volley, and I and J by the intraarterial injections of 200 microgrammes of acetylcholine and 10 microgrammes of nicotine, respectively (Eccles, Eccles and Fatt, 1956).

as "Flaxedil", decamethonium and "Mytolon"; but many anæsthetists still think that the original curare preparations, such as "Introcostrin", are the best. I should mention one other point of interest in this blocking pro-

experiments that could provide a crucial test between these theories, though the effect of acetylcholine injection seemed to be better correlated with the postulate of a blocking substance.

Another important disorder in neuro-muscular transmission is brought about by botulinum toxin, which kills by the paralysis brought on by blocking this transmission. The pure type A botulinum toxin shares with tetanus toxin the distinction of being the most toxic substance known. Brooks (1956) has shown in our laboratory at Canberra that the blockage of neuro-muscular transmission develops at the same time as a suppression of the spontaneous release of acetylcholine that gives the miniature endplate potentials. Apparently botulinum toxin acts on the nerve terminals, somehow "sealing" them so that the synaptic vesicles (Figure I) cannot pass across the surface membrane and effect the quantal release of acetylcholine.

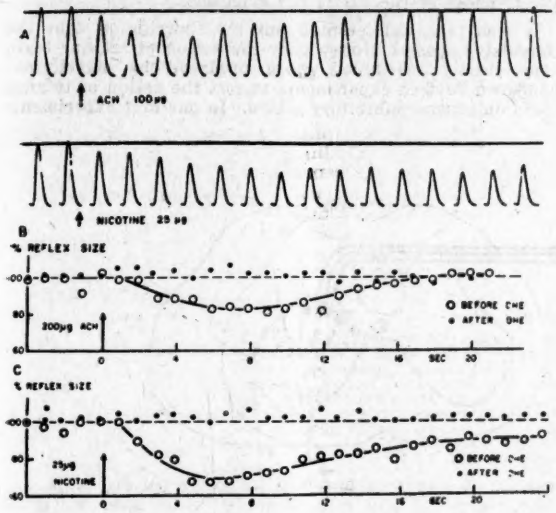

FIGURE IX.

A: Monosynaptic reflex spikes were evoked by the seventh lumbar dorsal root volleys at a frequency of one per second and recorded monophasically in the seventh lumbar ventral root. The individual spikes had a duration of about one millisecond, but the brief gaps between each represent about one second. In the upper series, the arrow signals close intraarterial injection of 100 microgrammes of acetylcholine, which results in a depression of the reflexes for about ten seconds. In the lower series, 25 microgrammes of nicotine sulphate produced a more profound and lasting depression, recovery occupying about sixty seconds. The horizontal lines were formed by the other beam, which was adjusted at the mean summit heights for a long series of reflex spikes immediately before the injection. B, C: The open circles plot measurements for series such as those of A, while the solid circles show the complete abolition of depression after the intravenous injection of 0·8 milligramme of dihydro-β-erythroidine hydrobromide per kilogram of body weight (Curtis, Eccles and Eccles, 1957).

Finally, before leaving the peripheral junctional systems, I should like to mention that acetylcholine is also responsible for transmission across synaptic junctions in sympathetic ganglia. Figure V shows the way in which curare can block transmission by so diminishing the depolarization of the ganglion cell that it fails to generate an impulse (R. M. Eccles, 1956). This blocking action of substances is of clinical significance in the treatment of hypertension, the usual blocking substance being C6 (hexamethonium), which works like curare. The success of such medication indicates that the hypertensions so benefited are due to a continuous discharge of vasomotor impulses along the sympathetic fibres.

When we come to the central nervous system the pharmacological story is much more obscure than in the simple peripheral junctions. Let us first look at some of the essential structural features in some detail. The motoneuron diagrammatically shown in Figure VI, A, has an axon going out to muscle fibres, and also has a great many branching dendrites. At higher magnification of Figure VI, B, we see its surface studded with little knobs on the ends of fibres that have come from other nerve cells, and at the still higher magnification that can now be attained with electron microscopy (Figure VI, C) the synaptic knob is filled with tiny vesicles, very like those seen in the nerve endings on muscle in Figure I. As at the neuro-muscular junction, the nerve terminal is in very close apposition ($^1/_{500}\mu$) to the surface of the nerve cell, so that the transmitter substances stored in the vesicles can be liberated into this narrow cleft in the closest proximity to their site of action when a nerve impulse causes these vesicles to burst on the surface (Palay, 1956), just as has been proposed for the neuro-muscular junction. The simplest reflex arc through the spinal cord, that for the tendon jerk, is illustrated in Figure VI, D, where the incoming dorsal root fibres are seen to end directly on motoneurons.

It has long been known that the axons of motor nerve cells give off branches as they are passing through the grey matter of the spinal cord on their way to the ventral roots. Recently, following up some remarkable work of Renshaw, who died from poliomyelitis some years ago in America, we (Eccles, Fatt and Koketsu, 1954) have been able to discover that these motor-axon collaterals end on the small nerve cells shown in Figure VII, A, which we have called Renshaw cells, and that these cells in turn send their axons back to the motoneurons which are inhibited thereby (cf. Figure XIII). Now there is a principle enunciated by Dale (1935) which I think is of the greatest importance in the whole story of chemical transmitters, and that is that any one nerve cell operates by the same kind of transmitter substance at all of its branches. It will readily be appreciated that the same chemical manufacturing goes on throughout the whole extent of a cell, and that a cell cannot make one kind of transmitter substance for some of its terminals and another kind for others of its terminals. Thus it would be expected that motor-axon collaterals would excite Renshaw cells by liberating acetylcholine, just as the other branches of these motor-axons do at the neuro-muscular junction.

Figure VII, B, illustrates some experiments on Renshaw cells which can be seen giving spike responses at high frequency when they are fired off by impulses in motor nerve fibres. A curare-like substance (dihydro-β-erythroidine) is seen greatly to depress their responses, while an anticholinesterase greatly prolongs their responses. For technical reasons it has been impossible yet to apply acetylcholine directly to the surfaces of these Renshaw cells; but we have done it by intraarterial injection through a cannula placed in the common iliac artery, all the other branches of the lower abdominal aorta being tied except the lumbar arteries. It was interesting to find that, when given in this way by injection into the spinal cord through the lumbar arteries, nicotine was a much more potent exciter of Renshaw cells than acetylcholine (Eccles, Eccles and Fatt, 1956), there being a difference of about 200 times in Figure VIII, B and C. So potent is this action of nicotine on Renshaw cells that it would be produced by the amount of nicotine absorbed from a few puffs of a cigarette. The anticholinesterase, eserine, which would stop acetylcholine from being destroyed by the cholinesterase, increased the potency of acetylcholine about tenfold without appreciably altering the response to nicotine (Figure VIII, F and G). On the other hand, the curare-like blocking drug depressed the effectiveness of both by a factor of 10 (Figure VIII, I, J.). All these results are attributable to the action of drugs on the cholinergic synapses which motor-axon collaterals make with Renshaw cells.

You will remember that synaptic actions in the central nervous system are of two kinds—excitatory, which tend to make cells fire impulses, and inhibitory, which tend to stop them. Most of the rest of this lecture will be related to the inhibitory transmitter story, because we hardly know anything about the pharmacology of the excitatory transmitters in the central nervous system, and pharmacology provides the clues that enable us to determine the nature of the transmitter substances. I mentioned earlier

that Renshaw cells acted as inhibitors of motoneurons, and I will describe experiments relating to this aspect of the Renshaw cell mechanism in order to show how difficult is the task of the pharmacological investigator in the central nervous system. Many have found that acetylcholine and nicotine depress the knee jerk, or, as we call it, the monosynaptic reflex. Figure IX, A, gives an example of this depressant action, in which nicotine and acetylcholine are injected intraarterially into the spinad cord. The reflexes are seen to be diminished within two seconds of the injection, and slowly recover. Now that we know that both acetylcholine and nicotine are potent in causing Renshaw cell discharges, which in turn inhibit motoneurons, it seems that this depressant action on tendon reflexes could be explained without postulating in addition that acetylcholine and nicotine depress excitatory synaptic action on motoneurons, which has been the usual conclusion drawn from observations like those of Figure IX, A. Experiments, such as the injection of the drug dihydro-β-erythroidine blocking Renshaw cell activity, action of strychnine. It can readily be appreciated that the virtual removal of inhibitory action would result in the unrestrained dominance of excitatory synaptic activity and hence of convulsions.

So far all types of inhibition that we have investigated have been depressed in precisely the same way by strychnine and the other related convulsant, brucein. However, all the modern synthetic convulsants that we have investigated have failed to depress inhibition. For example, NP 13, even in a large dose, has no action whatsoever (Curtis, 1956), and similar results were obtained with picrotoxin and "Metrazol" *et cetera*. Presumably such substances are effective by virtue of the increase in effectiveness of the excitatory synapses.

It was long ago pointed out by Sherrington that the convulsive spasms produced by the action of tetanus toxin very closely resembled those produced by strychnine; hence we devised experiments to test the action of tetanus toxin on central inhibitory action. In our first experiments

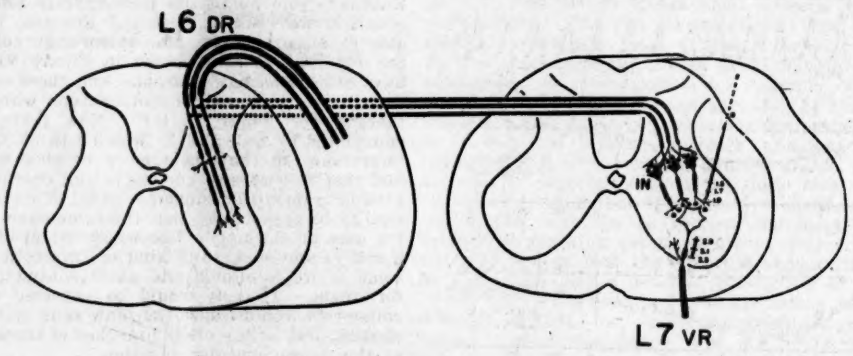

FIGURE X.

Diagram showing postulated direct inhibitory pathway from quadriceps fibres entering cord through the sixth lumbar dorsal root to a *biceps semitendinosus* motoneuron in the seventh lumbar segment. Collaterals from these Ia afferent fibres are shown running caudally to end synaptically on intermediate neurons (IN) in the seventh lumbar segment, which in turn send axons to converge on a *biceps semitendinosus* motoneuron. Excitatory synaptic knobs are shown by open circles and inhibitory synaptic knobs by solid circles (Eccles, Fatt and Landgren, 1956).

proved that our surmise was correct (Curtis, Eccles and Eccles, 1957), because, after such an injection, neither nicotine nor acetylcholine had any action on monosynaptic reflexes, as shown in Figure IX, B, C. Further evidence supporting our explanation was provided by the effect of strychnine, which, as we shall see, depresses inhibitory but not excitatory synapses, and also abolishes the effect of injected acetylcholine and nicotine.

Before I go on to discuss the central actions of convulsants such as strychnine and tetanus toxin, it will be appropriate to look at a diagram (Figure X) showing the simplest inhibitory pathway in the central nervous system (Eccles, Fatt and Landgren, 1956). Impulses from the annulo-spiral endings of quadriceps muscle are seen to run centrally along fibres which send branches down to the lower lumbar region, forming synapses there with a special kind of interneuron that inhibits the motor nerve cells supplying the antagonistic knee flexors. This so-called direct inhibitory action can be tested by its effect in depressing tendon or monosynaptic reflexes to the knee flexors. As is shown in Figure XI, A, such reflexes to the knee flexors are greatly diminished for a very brief time after the action of a volley of these inhibitory impulses from the knee extensors. When strychnine is given intravenously even in a subconvulsant dose (Bradley, Easton and Eccles, 1953), it greatly depresses this inhibition (Figure XI, B, C). This action is very rapid and highly specific. Furthermore, strychnine has virtually no action on the tendon reflexes themselves. A fairly extensive investigation of this specific action of strychnine makes it very likely that it accounts completely for the convulsant

(Brooks, Curtis and Eccles, 1956) the tetanus toxin was given by injection into one sciatic nerve, and the experimental tests were begun about twenty hours later before the clinical symptoms of local tetanus had started to develop in that limb. As in Figure XI, we determined

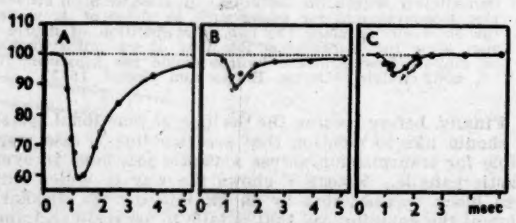

FIGURE XI.

A: Inhibitory curve plotting percentage of inhibitory action against time in milliseconds. B: Inhibitory curve after intravenous injection of 0·09 milligramme of strychnine per kilogram of body weight. C: Inhibitory curve after a further injection of 0·08 milligramme of strychnine per kilogram of body weight (Bradley, Easton and Eccles, 1953).

the time course of the depression that was produced by the action of a single inhibitory volley on a monosynaptic reflex. Already at twenty-one hours in Figure XII the inhibitory action was less than on the control side. Thereafter the inhibitory action was rapidly destroyed, so that virtually none remained when further tests were made at twenty-nine hours. The curves plotted in Figure XII

illustrate this progressive depression of inhibitory action, first on the left side and then on the right side, and concurrently the clinical signs of tetanus could be seen developing. In further experiments we confirmed the general belief that tetanus toxin spread up nerve pathways at the relatively slow rate of about five millimetres an hour and entered the spinal cord through the dorsal and ventral roots.

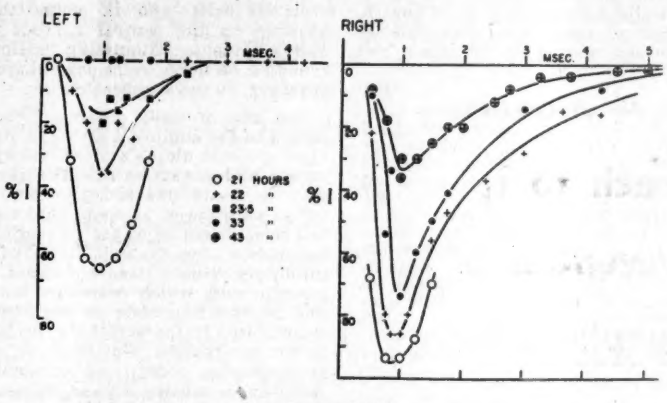

FIGURE XII.

Curves as in Figure XI, showing time courses of direct inhibition of monosynaptic reflex from *biceps semitendinosus* motoneurons of the spinal cord under "Nembutal" anæsthesia. The symbols denote the inhibitory effects observed at the times indicated after the injection of tetanus toxin in 0·05 millilitre of normal saline under the sheath of the left sciatic nerve at the mid-thigh level. Curves were obtained on the left and right sides, respectively. Each plotted percentage is the mean of 10 to 20 observations (Brooks, Curtis and Eccles, 1955).

A more precise study of the mode of action of tetanus toxin has been made by injecting it into the spinal cord close to the motor nerve cells (Brooks, Curtis and Eccles, 1957). Under such conditions, the onset of the inhibitory depression occurs in only a few minutes after injection of the toxin, and it rapidly progresses, as shown in the series of Figure XIII. The slow movement of tetanus toxin through the spinal cord has been revealed by experiments in which tetanus toxin was injected into the spinal cord, and the time course of depression of inhibition was determined for three sets of motor nerve cells which lay at progressively deeper layers in the spinal cord. It is possible in this way to measure the velocity of movement of tetanus toxin through the spinal cord. It certainly is very slow transversely, taking several hours to move one millimetre; but our experiments indicate that it moves much more rapidly longitudinally in the spinal cord, just as it does in peripheral nerves. When very small quantities have been injected, it has been found that the depression of inhibitory action is reversible over many hours.

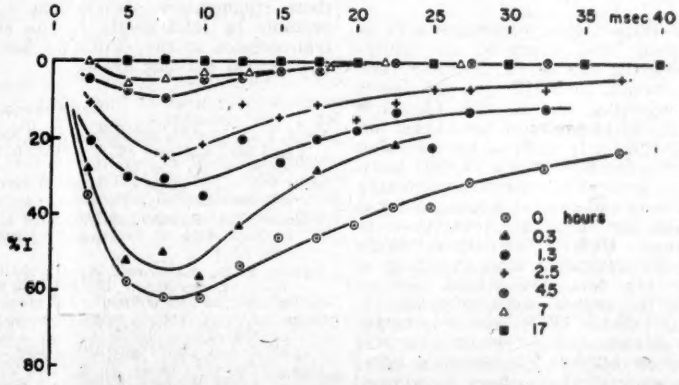

FIGURE XIII.

Inhibitory curves constructed as in Figures XI and XII. The curves plot the percentage inhibition of the monosynaptic reflex from *flexor digitorum longus* motoneurons by antidromic volleys propagated from the motor fibres of *biceps semitendinosus*, gastrocnemius and plantaris nerves (pathway as in Figure VIIA) at various times after an intraspinal injection of L61 toxin (Brooks, Curtis and Eccles, 1957).

I think we can claim, therefore, that these experiments have shown that we need postulate only one action for tetanus toxin, at least when it is given in clinically significant doses, and that is a depression of inhibitory synaptic action. We have been able to show, furthermore, that this depression is not exerted at any point along the inhibitory pathway—for example, on the interneuron that is always present (Figures VIIA, X and XIV)—but only at the actual inhibitory synaptic terminals. Thus its site of action must be very close to that of strychnine, as illustrated in Figure XIV.

Our present hypothesis is, however, that tetanus toxin acts like botulinum toxin in somehow sealing the mem-

brane around the synaptic knobs so that the vesicles of transmitter substance cannot penetrate it and exert their action on the post-synaptic membrane. These two toxins are both the products of clostridia and are the most toxic substances known. For example, van Heyningen (1950) states that the minimum lethal dose of either toxin in the pure form is less than one-millionth of a milligramme for one kilogram of guinea-pigs. By comparison, diphtheria toxin is 400 times less potent, and cobra venom 1000 times less potent. Such fantastically high potency is, of course, easily intelligible in the light of observations that indicate the extremely localized actions exerted by botulinum and tetanus toxins.

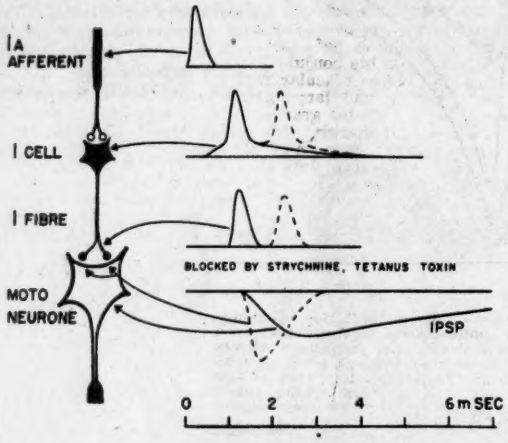

FIGURE XIV.

Schematic drawing of the anatomical and physiological features of the direct inhibitory pathway. It shows the events in the primary afferent fibre, in its excitatory synaptic connexions with an intermediate neuron (I cell), and finally in the inhibitory synaptic connexion of this neuron with a motoneuron, where the inhibitory subsynaptic current is shown by a broken line and the inhibitory potential by a continuous line (Eccles, 1957).

On the other hand, we suspect that strychnine acts in the central nervous system like curare at the neuromuscular junction in occupying the special receptor sites on the post-synaptic membrane, so preventing the transmitter substance from adhering thereto and becoming effective. Admittedly, these suggestions are based on analogy and cannot be tested directly until we have isolated the inhibitory transmitter substance. Work on this isolation has been pursued in several laboratories, including our own, and there have been claims that a substance has been isolated which acts as the inhibitory transmitter in the central nervous system. Unfortunately these claims have been based upon very optimistic interpretations of inadequate experiments. In fact, the whole field of chemical transmitters in the central nervous system is virtually an unknown one (Eccles, 1957), and only in the one place that I have described (acetylcholine at the synapses made by motor-axon collaterals on Renshaw cells) has the transmitter at a central synapse been ascertained with any degree of assurance.

It is now being widely realized that transmitter substances of the central nervous system provide one of the most important research topics in biology, and for that matter in medical science. Intensive work is developing in many places. At the International Physiological Congress in Brussels in 1956, about one-fifth of the total space devoted to symposia was occupied by contributions on physiological and pharmacological investigations relating to these transmitter substances. There may be only one inhibitory substance in the vertebrate nervous system, but almost certainly there are several synaptic excitatory substances. If we could discover the chemical nature of these substances, it would be possible to develop a rational pharmacology utilizing these substances themselves and their analogues, or other substances designed to modify their activity. At present the only pharmacological agents whose central actions can be correlated with transmitter mechanisms are tetanus toxin, strychnine and brucein acting on the inhibitory synapses, and anticholinesterases, the curare-like blocking substances and nicotine acting on the cholinergic synapses on Renshaw cells. However, it is probable that many other as yet unidentified cholinergic synapses exist, and no doubt the attractive effects of nicotine on the central nervous system are due to its highly potent stimulating action on the cholinergic synapses of nerve cells somewhere in the higher centres, probably in the cerebral cortex.

You are probably aware of the great development in regard to the empirical action of such substances as LSD 25 (lysergic acid diethylamide), chlorpromazine and reserpine on the higher centres (Bein, 1956), but as yet it is impossible to relate this action to the operation of any transmitter substances, as could be done if 5-hydroxytryptamine had been proved to be the transmitter substance at specified synapses. For example, if 5-hydroxytryptamine was an inhibitory transmitting substance, the psychotic action of lysergic acid, which resembles that of mescaline, could be due to its antagonism of the 5-hydroxytryptamine, which is exhibited in the peripheral preparations, rabbit intestine or rat ear vessels. Furthermore, reserpine could exert its tranquillizing action and antagonism to lysergic acid by its effect in causing a great release of 5-hydroxytryptamine as described by Brodie, Pletscher and Shore (1956). There is evidence that these actions of lysergic acid and reserpine are mainly exerted on hypothalamus and the brain-stem, probably on the cells of the reticular formation, and very little on the cerebral cortex (Bein, 1955, 1956; Schneider, Plummer, Earl and Gaunt, 1955). For example, it is stated that the intellect is unimpaired and the orientation is normal. Thus tranquillizers like reserpine and chlorpromazine do not produce a general sedative effect, but rather have a selective action. Chlorpromazine also has a selective action in that it depresses the activation of the small or γ motoneurons that supply the muscle spindles, while the pathway to the large or α motoneurons is unimpaired (Henatsch and Ingvar, 1956). Another selectively acting drug is mephenesin, which specially depresses the synaptic stimulation of interneurons. No doubt all these fragmentary observations will eventually be interpretable in relationship to the substances that mediate transmission at the excitatory and inhibitory synapses of the central nervous system.

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CLINICAL AND EPIDEMIOLOGICAL OBSERVATIONS ON DENGUE FEVER IN QUEENSLAND, 1954–1955.

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AN outbreak of dengue occurred in Townsville in the period January to April, 1954, and is estimated to have affected 15,000 people in a total population of 40,000 (Rowan, 1956). Similar cases occurred in the area served by the Innisfail Field Station of the Queensland Institute of Medical Research from March, 1954, to May, 1955. The clinical and epidemiological features of 75 patients referred to the Field Station and finally diagnosed as dengue fever are analysed in the present paper.

Diagnosis.

Standard serological tests were performed at the Laboratory of Microbiology and Pathology, Brisbane, on paired samples of serum to exclude leptospirosis, scrub, tick and murine typhus, Q fever, brucellosis, typhoid and paratyphoid. Serological tests against dengue and related viruses, which are referred to below, supported the diagnosis in a number, but gave negative results in other clinically typical cases. The clinical picture and to a lesser extent the epidemiological features have therefore been the main diagnostic criteria by which patients have been included in the series.

Clinical Features.

The clinical features recorded in the 75 patients and their incidence are as follows: headache, 62; generalized muscular pain, 41; vomiting, 20; cough, 19; sore throat, 11; sore eyes, 34; subjective neck stiffness, 8; frequency of micturition, 2; dysuria, 4; retention of urine, 1; rash, 31; lymph gland enlargement, 47; faucial injection, 17; conjunctival injection, 15; bradycardia, 15; objective neck stiffness, 12; liver tenderness, 10; abnormal chest signs, 5; splenomegaly, 1; enanthem on palate, 2. A minority showed the classical picture of dengue, with rash, bradycardia, leucopenia and biphasic temperature chart. The disease was more frequently seen as a short febrile illness with few distinctive features, and was therefore often difficult to distinguish clinically from the indigenous fevers of North Queensland. Leptospirosis, in particular, was often difficult to distinguish from dengue. Mild cases of dengue with a rash simulated rubella, as has been described in previous series (Lumley and Taylor, 1943).

The following case histories exemplify the variations seen.

A., aged twenty-nine years, a millworker, of Goondi (near Innisfail), was admitted to the Innisfail District Hospital on July 21, 1954. He had been ill since the previous day with headache, backache, pain in his legs, sore eyes and vomiting. On examination, his conjunctivæ were injected, his neck was stiff, he had a fine macular rash on his trunk, his face was flushed, and he had large glands palpable in his axillary, inguinal and occipital groups. He was tender to palpation under his costal margins, his fauces were injected, his temperature was 101·4° F., and his pulse rate 92 per minute. He was still very ill on July 22; his rash was more prominent, with pink macules on his limbs, and he complained of a sore throat. His white cell count was 2100 per cubic millimetre (50% neutrophile cells, 48% lymphocytes and 2% monocytes). The subsequent course of his illness is shown in Figure I.

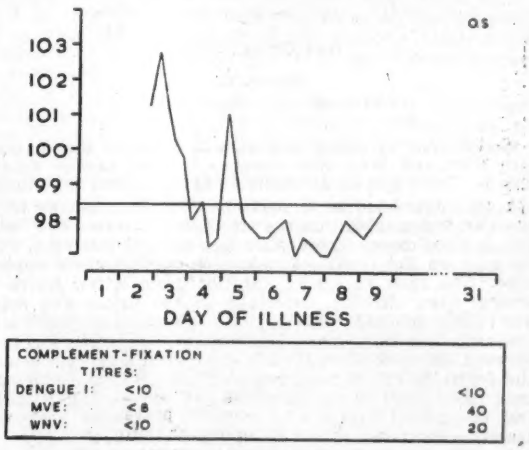

FIGURE I.
Temperature chart of A., showing biphasic course.

His temperature rose again to 101° F. on July 24; the pulse rate at the time was 60 per minute. He was discharged from hospital well on July 29.

Examination of paired sera showed a definite rise in the level of complement-fixing antibodies against Murray Valley encephalitis (MVE) antigen, a slight rise against West Nile antigen, and no reaction against dengue type 1 antigen.

The following patient had no rash, but the diagnosis was suggested by lymph gland enlargement and bradycardia, and supported by serological tests.

B., aged twenty-seven years, a building contractor, of Innisfail, was admitted to the Innisfail District Hospital on February 23, 1955. He had fallen ill on February 22 with headache, malaise, feverishness, sore eyes and anorexia. On examination, his temperature was 101·8° F., and his pulse rate 78 per minute; he had large inguinal and axillary glands, and his eyes were injected. No other abnormalities could be found on physical examination. The subsequent course of his illness is shown in Figure II; his temperature fell to normal on the second day after admission, and he was discharged on February 27. His pulse rate ranged from 48 to 64 per minute during convalescence.

A striking rise in antibody titre was demonstrated against MVE antigen; his sera were not tested against West Nile or dengue type 1 antigens.

The following patient was diagnosed clinically as having leptospirosis on his admission to hospital; he had some lymphadenopathy, but none of the other classical features of dengue.

C., aged forty-one years, a cane farmer, of Garradunga (near Innisfail), was admitted to the Innisfail District Hospital on April 30, 1954. He complained of headache and malaise for one day, with pains in his legs and sore eyes. He had no vomiting, and no urinary or respiratory symptoms. On examination, his eyes were injected and his face was flushed; he had no rash or eschar; he had abrasions on his left arm and his feet, and enlarged tender glands in his axillæ and left groin. He was tender to palpation under his right costal margin. The subsequent course of his illness is shown in Figure III; he complained of a sore throat on May 1, and was discharged from hospital on May 4.

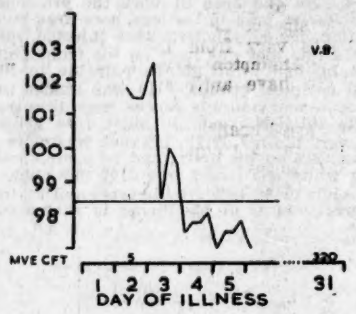

FIGURE II.
Temperature chart of B.

Examination of paired sera showed a rise in titre against both MVE and West Nile antigens, but not against dengue type 1. There was no development of leptospiral agglutinins.

A rash developed in 31 patients. This was usually pink, macular and maximal on the trunk, but involved the limbs also in most cases. The flushed face and injected eyes, with the rash on the trunk, often gave a characteristic appearance. The rash varied in duration from a few hours to several days; itching, especially of the palms and soles, was often noticed, and sometimes preceded the rash; desquamation occurred occasionally. The rash appeared between the second and sixth days of illness, the second and fourth being the most frequent. One patient (a woman, aged forty-seven years) developed petechiæ on her ankles and the dorsal aspect of her feet. A similar rash was described by Sabin (1952) and Stewart (1944).

Two patients had small erythematous areas with a few petechial spots on their palates. These may have represented the enanthem of dengue (Lumley and Taylor, 1943).

Enlargement of lymph glands was recorded in a majority of the series; in many cases the enlargement was generalized, involving cervical, inguinal and axillary glands. The glands subsided rapidly in convalescence. One patient had a palpable spleen.

One-quarter of the series had injected fauces, and most of these complained of a sore throat. A dry, non-productive cough was present in 19 patients.

Generalized muscular pains were common. These were particularly severe in limbs, but some of the tenderness found on abdominal palpation may have been muscular in origin. It was common for patients to require morphine to obtain relief from their muscular pains. Joint pain was common, but no joint swelling was seen. A number of patients had definite resistance to neck flexion, but this also was considered to be due to muscle spasm, and lumbar puncture was not performed on any patient.

Bradycardia occurred in 15 patients, shown either in a discrepancy between fever and pulse rate, or in absolute bradycardia during convalescence. This was therefore not a usual feature in the series.

White cell counts were performed on 22 occasions, from the second to the ninth days of illness. The counts ranged from 2000 to 8000 per cubic millimetre, and were below 5000 in 12 cases. Differential counts gave distributions within normal limits.

The total duration of fever averaged 4·5 days; it ranged from two to seven days, with two extreme values of eight and ten days. Biphasic temperature charts occurred in 16 patients, with two distinct peaks of fever; in ten of these the final peak of fever was preceded by an afebrile period of duration varying from a few hours to several days.

Laboratory Investigations.

Blood from 29 patients, collected early in the illness, was inoculated into 21-day-old mice, usually both intracerebrally and intraperitoneally. The blood from 14 patients was inoculated also into day-old mice. Some of the inoculations were carried out at Innisfail as soon as possible after the blood was collected; some, including those into infant mice, were carried out by Mr. J. H. Pope in Brisbane with blood maintained meanwhile on dry ice. Four blind passages were routinely made, but in no case was a virus isolated.

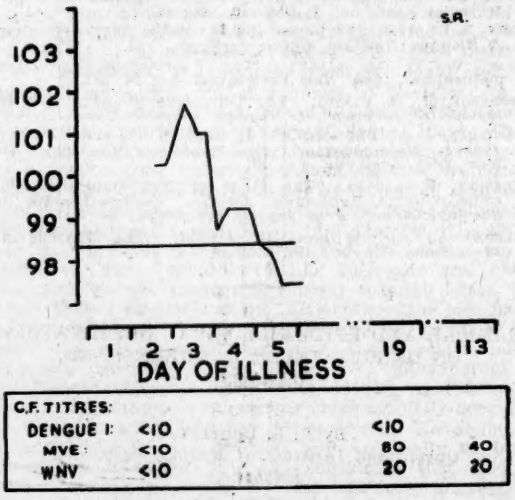

FIGURE III.
Temperature chart of C.

Paired samples of serum from 23 cases and single samples from five were examined at the Commonwealth Serum Laboratories by Dr. J. L. O'Connor and Dr. L. C. Rowan for complement fixation against dengue 1 antigen, and also when the amount of serum permitted against MVE and West Nile antigens. Antibodies to one or more antigens were demonstrated in 11 cases, or 39%. A fourfold rise showed in six patients, and five more showed a convalescent titre of 1:20 to 1:160. The proportions of results positive with the individual antigens were: dengue 1, 4/28; MVE, 8/23; West Nile, 5/10. Dr. Rowan comments that these results indicate the broadness of the complement fixation response among this virus group. The low figure for dengue 1 may be explained by the weakness of the antigen that was then available.

Paired samples of serum from 64 cases, and single samples from eight were examined at the Queensland Institute of Medical Research by C. G. Ludford and I. Cook for complement fixation against MVE antigen. In 27 patients, or 37·5%, antibodies were found to a titre of 1:20 to 1:320; in 18 of these there was at least a fourfold rise (Ludford and Cook, 1957).

Thus, between one-third and one-half of the cases tested showed a significant production of antibodies to one or other antigen of the dengue group; MVE antigen was the most frequently employed. When the serological result was positive it gave support to the diagnosis of dengue.

However, no clinical difference was apparent between the cases in which the serological result was positive and those in which it was negative.

There was no evidence of Murray Valley encephalitis in the Innisfail district in 1954-1955, but the serological pattern of some individuals in this series may conceivably have been influenced by contact with the MVE virus when it was active in North Queensland in 1951.

Epidemiology.

The time incidence of the 75 patients whose clinical features have been discussed is shown in Figure IV. The figure shows that 27 fell ill in the period March to May, 1954, and 40 in the period October, 1954, to May, 1955. The winter months of 1954 produced only eight cases.

The geographical distribution is also shown in Figure IV. Of the 45 infected in the Innisfail area, 20 were at the village of Flying Fish Point, four miles from Innisfail. An outbreak there was responsible for the increase in incidence in October to December, 1954; it preceded the second peak in incidence at Innisfail town, which commenced in January, 1955.

The 30 patients infected in areas outside Innisfail include one from Ingham, nine from the Tully area, six from Babinda and its district, eight from Gordonvale, two

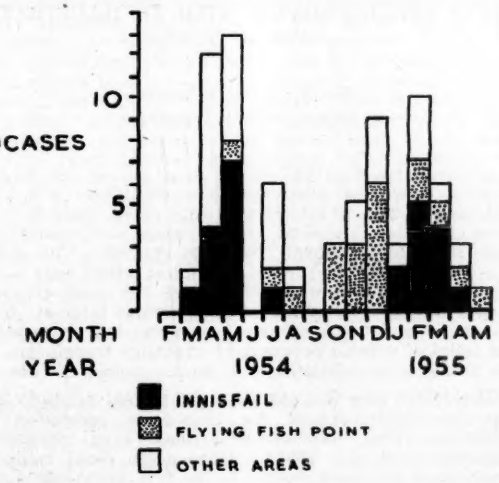

FIGURE IV.
Monthly distribution of the 75 cases.

from the Cairns area, one from the Mossman area, two from Townsville, and one from Ayr. These numbers reflect the bias due to the location of the Field Station, but it is of interest that no cases were recognized at Babinda (where case reporting was as complete as possible) during the April-May, 1954, period, when a number of cases occurred at Innisfail, 20 miles south, and at Gordonvale, 20 miles north. The first case there occurred in December, 1954, and six were diagnosed between then and April, 1955.

The ages of the patients ranged from seven to sixty years. Children (fifteen years or younger) accounted for 23, and the average age was twenty-four years. Included in the series are 26 women. There was no demonstrable difference in age, sex, time or geographical incidence between the groups that developed serological evidence of infection and those that did not.

These data may be correlated with the behaviour of the dengue fever outbreak elsewhere in Queensland. The earliest case recognized (in retrospect) at Townsville occurred at the end of November, 1953, and the presence of an epidemic was realized in January, 1954. The peak incidence occurred in February, and the outbreak subsided in May after involving almost 40% of the population. Cairns had an outbreak in April and May, 1954, with cases occurring until July; it is estimated that not more than 10% of the community were infected. Dengue fever occurred there again in the early months of 1955, when a smaller number of cases occurred. Mareeba and Ingham had outbreaks in April-May, 1954, involving only a small proportion of the population. Ayr was affected from February to May, 1954, and Bowen early in 1954, Mossman, where a case was diagnosed in August, 1954, had an outbreak from February to June, 1955.

The disease was widespread in Central Queensland in the summer of 1954-1955, epidemics being reported from Emerald (where it prevailed in December and January), Springsure (December, January), Rockhampton (January to March), Biloela (January), Alpha (December to April), Jericho (February, March), Barcaldine (February), and Gladstone (April to June). No exact data are available concerning the size of these outbreaks, but estimates of the attack rates vary from 15% to 75%. Patients at Biloela and Rockhampton were shown by Ludford and Cook (1957) to have antibodies in high titre against MVE virus.

Brisbane remained unaffected, although each of the seven previous outbreaks of dengue in North Queensland since 1895 had been followed by a high incidence in Brisbane. There were no admissions to the Brisbane Hospital for dengue in 1954, two in 1955 (in April and May, both patients being recent arrivals from Central Queensland), and one (a doubtful case) in February, 1956. These figures may be contrasted with those for the previous outbreak; there were 116 admissions to the Brisbane Hospital for dengue from February to July, 1942, and 87 from January to June, 1943.

Dr. J. D. O'Connor of Lismore, in northern New South Wales, informed me in May, 1956, that dengue had not been reported in that district in the last three summers.

Discussion.

Queensland has been subject to periodic epidemics of dengue, the previous one occurring in 1941-1944. No cases were recognized from the war years until the present epidemic commenced. One might expect this interval to

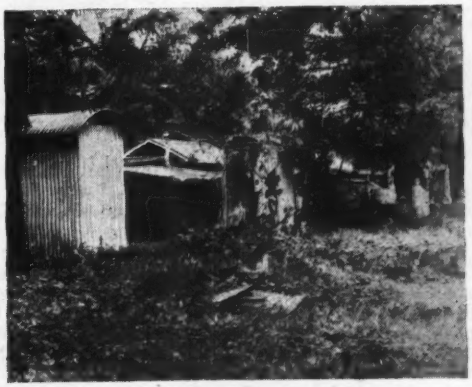

FIGURE V.
The main street of Flying Fish Point, showing the low standard of housing, water tanks and litter on edge of road.

have caused a fall in immunity sufficient to render the population susceptible; the low attack rates in many areas are therefore unexpected and welcome. While previous epidemics extended to northern New South Wales, the present outbreak reached only to Central Queensland. As regards possible explanations for this behaviour, Lumley and Taylor (1943) list the following as influencing attack rates: the proportion of non-immunes in the population; the vector density; the population density; the properties of the virus; and climatic factors.

Innisfail and Flying Fish Point would not be expected to differ in immunity, climate or infecting virus, but the former had 25 cases in a population of 6600 and the latter 20 in 232. These figures of course are incomplete, as many patients may not have sought medical advice and others may have been treated at home. Even with these reservations, the difference in incidence is striking. Flying Fish Point acts as a low class residential area for people employed in Innisfail, four miles distant. The standard of housing is low, the water supply is from rain tanks, and the sides of the roads and vacant areas have been used as rubbish dumps (Figures V and VI). Thus, broken

FIGURE VI.
A typical backyard at Flying Fish Point; two boys living here are included in the series.

coconuts, empty tins, unscreened tanks, blocked guttering *et cetera* provide numerous breeding places for *Aëdes ægypti*. Innisfail has a higher general standard of housing, an excellent water supply and few rainwater tanks. No mosquito population studies were done (except to confirm that *A. ægypti* was present in both places), but it seems reasonable to explain the differences in incidence of dengue by variations in vector density. A similar factor may have influenced the attack rates in other towns in Queensland.

Dr. M. J. Mackerras informs me that in November, 1954, *A. ægypti* was numerous in Townsville. In August, 1955, Dr. I. M. Mackerras noted that it was present, but comparatively infrequent, in Ingham, Innisfail and Cairns. It has disappeared from Brisbane in recent years, and this explains the freedom of this city from dengue on this occasion.

Summary.

1. Of the patients referred to the Innisfail Field Station of the Queensland Institute of Medical Research in the period March, 1954, to May, 1955, 75 were finally diagnosed as having dengue fever.

2. The disease presented as a febrile illness lasting from two to seven days, with headache and muscular pains, and with marked prostration in the more severe cases. Lymph gland enlargement was the commonest abnormality found on physical examination. Rash, bradycardia and biphasic temperature chart were seen in a number, but many had no specific clinical features.

3. The demonstration of complement-fixing antibodies in significant titre against antigens of the dengue group —particularly Murray Valley encephalitis antigen—gave support to the diagnosis in between one-third and one-half the cases tested.

4. Blood from 29 patients was inoculated into mice, but no virus was isolated.

5. The much higher relative incidence at Flying Fish Point than in Innisfail is ascribed to the presence in the former of rain tanks and rubbish dumps, which provide facilities for the multiplication of *A. ægypti*.

6. The city of Brisbane, from which *A. ægypti* is now absent, escaped the outbreak. This is noteworthy, as Brisbane had a high incidence in past invasions of Queensland by dengue.

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ACUTE RENAL FAILURE, WITH AN ILLUSTRATIVE CASE HISTORY.

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ACUTE RENAL FAILURE occurs in a variety of medical, surgical, urological and obstetrical conditions, and has a mortality of 20% to 50% in published cases. Only in recent years has the mechanism of its onset and course been understood and rational treatment applied. This article has been written to present the latest views, and a case history is included which illustrates the main course of events and has three features of particular interest. These are the effect of "Resonium-A" on potassium intoxication, the relief of uræmic pre-coma by exchange transfusion, and the response to restricted fluid intake during the diuresis.

The doctor who first examines the patient needs to know the remediable causes, for immediate correction will minimize renal damage, and may even prevent it (Blackburn *et alii*, 1954). Once acute renal failure is established, the main danger in the first week lies in over-treatment with such simple poisons as water, salt and protein.

Subjects affected are frequently young and otherwise healthy, and will recover adequate renal function if they survive the danger period of three to four weeks. Thus the responsibility for the management of these patients is great, and if transportation is practicable, should be borne by a medical unit well versed in their treatment. Suitable laboratory aid and special equipment should be available, and if possible an artificial kidney for extracorporeal hæmodialysis. Hæmodialysis has a very real place in supplementing conservative management. Of course it cannot modify the lesions in the renal tubules, but it is used when the biochemical abnormalities which result are a threat to life or sufficient to delay recovery.

DEFINITION.

Acute renal failure exists when renal excretory function is suddenly diminished and urine flow remains below 400 millilitres per day. This is usually due to acute tubular necrosis with interstitial œdema and altered hæmodynamics. Various names have been used, including anuria, lower nephron nephrosis, crush syndrome, hepatorenal syndrome, shock kidney, traumatic uræmia, and toxic nephrosis. The oliguric phase, which may persist for three weeks or even longer, is followed by diuresis for some days, and then there may be polyuria for several weeks.

ÆTIOLOGY.

The many causes vary widely, and they can produce acute renal failure varying in degree from a slight fall in urinary output with a small temporary rise in the level of urea in the blood to severe oliguria or anuria with progressive uræmia and death. Remediable causes are the following: (i) circulatory failure, as may occur with excessive losses of water and electrolytes, hæmorrhage, or myocardial failure; (ii) intravascular hæmolysis—for example, mismatched blood transfusion, urological operations in which tap water is used for bladder irrigation, severe malaria, and septicæmia due to *Clostridium welchii*; (iii) nephrotoxins—for example, sulphonamides and mercuric chloride; (iv) acute pyelonephritis; (v) ureteric obstruction.

PATHOGENESIS.

The term "lower nephron nephrosis", though commonly used, is inaccurate. The renal lesions are not confined to the distal tubule, but are scattered throughout the length of the nephron, including the glomerulus (Oliver *et alii*, 1951). Not all nephrons are affected, for many areas may escape damage and remain structurally normal, although their function may be impaired by the pressure of interstitial œdema affecting filtration pressure and renal blood flow. Two types of lesions are described. Those due to nephrotoxins involve the epithelial cells of the proximal tubule, while ischæmia causes patchy necrosis and rupture of the basement membrane as well as of tubule cells throughout the whole length of the nephron. With the latter type of lesion it is thought that the tubular contents, which should pass on as urine, escape into the interstitial spaces of the kidney causing œdema which impedes renal blood flow. Renal vasoconstriction also occurs, as after intravascular hæmolysis. Such lesions occur at the onset of acute renal failure and continue to occur until the initiating cause is removed. Recovery then proceeds. Renal function is usually restored adequately in two or three weeks, but during the ensuing six to twelve months most tubules with severely disrupted basement membranes become occluded and lost, while others with less severe lesions may continue to regenerate (Oliver, 1953). These tubules frequently pass urine which is hypotonic, so that a "water-losing nephritis" may persist for several months even though the patient appears to be in good health.

CLINICAL COURSE AND TREATMENT.

The clinical course is usually divided into three phases: the oliguric phase, during which less than 400 millilitres of urine are passed per day; the early diuretic phase, when the daily urinary output exceeds 400 millilitres and may reach several litres; and the late diuretic phase, when the diuresis is subsiding to a steady output of 1500 to 3000 millilitres per day.

Oliguric Phase.

The oliguric phase is due to an organic lesion of the renal tubule which takes some time to heal; in the meantime, the lack of adequate urinary excretion is liable to result in widespread disturbances in various bodily systems.

Cardio-Vascular System.

Unless adequate precautions are taken to prevent the accumulation of water, sodium and potassium in the body, over-hydration to the extent of 10 litres or more may occur; this will be discussed later.

Gastro-Intestinal System.

Nausea, anorexia and vomiting are sometimes so distressing that oral feeding becomes impracticable. Distension is common, and combined with poor wound healing may cause a burst abdomen in surgical cases. Hæmodialysis clears the above-mentioned symptoms, so that oral feeding can be recommenced.

Nervous System.

Somnolence, stupor and mild delirium are common and may progress to coma. Muscular twitching and convulsions are due to uræmia, to a low level of ionized calcium and sometimes to hypertensive encephalopathy. Although the cerebral blood flow in uræmia is usually normal, oxygen consumption is reduced, so that other chemical abnormalities probably also affect cerebral metabolism. The sensorium is often cleared dramatically by hæmodialysis, or by exchange transfusion.

Blood.

Moderate neutrophile leucocytosis is usual even in the absence of infection. A close watch must be kept for infection, as fever is variable and is not a reliable sign. Antibiotic therapy may be necessary but in reduced dosage, since renal excretion has failed. Normochromic normocytic anæmia is invariably present. The hæmoglobin content often falls fairly rapidly to six to eight grammes per 100 millilitres of blood (the hæmatocrit to 20% to 25%), and then remains at this level during the oliguric phase, gradually to rise during the months of convalescence. Two factors appear to play a part in causing the anæmia. There is a depression of erythropoiesis as indicated by the sparsity of erythroblasts in the bone marrow and by the depressed uptake of iron, and there is hæmolysis probably due to some factor in the plasma. Transfused cells have a short survival, the hæmatocrit dropping back to 25% in a few days, whereas the patient's own red cells show normal survival when transfused into a normal person. Since transfused cells relieve the anæmia for only a short time, and the patient does not often appear to be distressed by the anæmia, blood transfusions are infrequently indicated. Pulmonary œdema and congestive cardiac failure are a greater danger, and these are sometimes induced by the added load of water and sodium consequent upon transfusion.

Chemical Abnormalities.

Chemical abnormalities relate to alterations in the volume of body water, in acid-base equilibrium, and in the concentration of sodium, potassium, calcium, phosphate, urea and creatinine.

Body Water and Sodium.—The control of body water and sodium frequently errs on the side of over-hydration and excess sodium intake, with resultant gain in weight and pulmonary congestion together with the danger of congestive cardiac failure and acute pulmonary œdema. The endogenous formation of water from the oxidation of administered glucose and from protein and fat metabolism should not be forgotten, since a man of average size derives, while oliguric, approximately 600 millilitres per day in this way. It is to water similarly derived from catabolism of its fatty hump that the camel owes its endurance in the desert. Water replacement in the anuric patient should thus be limited basically to 400 millilitres per day (13 ounces); this, together with the endogenous water, will just provide for the daily losses in the breath and from the skin. Extra intake will be required to counterbalance any other losses as from fistulæ, by drainage, in vomitus, through diarrhœa, and in frank sweating. The daily recording of body weight is a simple and valuable check on the state of hydration. A progressive fall of about one pound per day (0·3 to 0·4 kilogram per day), or more if the caloric intake is poor, is to be expected while hydration remains normal. The serum sodium level tends to fall during oliguria, particularly if over-hydration occurs, and even if the total amount of sodium in the body is increased. It probably migrates into the cells, owing to their impaired functions. Sodium administered in the oliguric phase should be restricted to an absolute minimum, unless severe diarrhœa or paralytic ileus is present, when losses should be replaced. Excess water and salt can be removed by ultrafiltration by the use of the Alwall-type dialyser.

Acidosis.—Acidosis is common, owing to the retention of acid metabolites and sometimes to sodium loss as well. Alkaline solutions of sodium bicarbonate, lactate or acetate should be used very cautiously, owing to the danger of producing tetany or pulmonary œdema. Hæmodialysis is the only rational method of correcting acidosis, in that it removes the acid metabolites.

Calcium and Phosphate.—Hypocalcæmia and hyperphosphatæmia increase gradually. Tetany is uncommon unless

alkali is given. Calcium infusions are only of temporary value, since the mechanisms underlying the hypocalcæmia are unchanged. Daily intravenous infusions of 100 millilitres of 10% calcium gluconate solution are necessary to raise the level towards normal, and may be necessary to counteract high potassium levels when other treatment is unavailable. The serum magnesium level is also raised.

Nitrogen Retention.—Urea and creatinine levels rise fairly rapidly from the onset of oliguria, and are useful early signs. High levels are apparently non-toxic *per se*, but toxic levels of ammonia may be produced from urea.

Potassium.—Dysfunction of cardiac and smooth muscle due to serum potassium levels above 7·0 milliequivalents per litre is one of the main dangers of acute renal failure. The symptoms and signs of hyperkalæmia include anxiety and restlessness leading to stupor and convulsions; weakness, hyporeflexia and paræsthesiæ, then paralysis and areflexia, including respiratory paralysis; bradycardia, falling blood pressure, and faint heart sounds followed by arrhythmia, periods of asystole and circulatory collapse. These develop only at dangerous levels of potassium; an earlier sign is peaking and elevation of the *T* wave in the electrocardiogram, with prolongation of the *Q-T* interval. *QRS* changes and arrhythmias appear very late, and may be too late. Repeated estimations of the potassium level in serum by the use of a flame photometer are essential for controlling hyperkalæmia, as treatment can then be commenced before dangerous levels occur. An electrocardiogram should be taken daily. The rate of development of hyperkalæmia varies considerably from case to case, depending on the amount of potassium ingested (milk and orange juice are rich in potassium) and on the rate of liberation of potassium from cells—for example, from red cells in hæmolysis or hæmorrhage and from traumatized muscle cells. Organized therapy is essential if the serum potassium level exceeds 6·0 milliequivalents per litre, and it should be regarded as an emergency if electrocardiographic or clinical signs are obvious. Hyponatræmia and hypocalcæmia aggravate hyperkalæmia. The methods of treatment available are as follows: (i) Infusions of 100 to 250 millilitres of 2·5% saline may be given. The effect is immediate, but lasts only two hours, and this procedure is liable to overload the patient with sodium. (ii) Glucose and insulin give temporary results in half to one hour, lasting only four to six hours. (iii) Cation exchange resins saturated with sodium or ammonium ions—for example, "Resonium-A"—may be used. These are given by mouth or as an enema and are effective in only some patients. (iv) Digitalization helps to antagonize the effect of potassium on the heart, without actually lowering the serum level; but it should be remembered that calcium infusions enhance the effect of digitalis. (v) Hæmodialysis with an artificial kidney is very effective in removing potassium from plasma, and also tends to correct hypocalcæmia and hyponatræmia. This should be used when simpler methods fail, or when the condition has occurred early in oliguria with a steadily rising serum potassium level. The best treatment of potassium intoxication is prophylaxis.

Caloric Intake.

Bull's regime, consisting of an emulsion of oil, glucose and water given orally, is satisfactory in a few cases, but is distressing to most patients in that it causes nausea and vomiting. Glucose and fructose are by far the most important foods for preventing protein catabolism, and at least 100 grammes should be given daily, either orally in the form of sweets, lemonade, ginger-ale, rice or other foods free of potassium, sodium and protein, or intravenously. Solutions of glucose (25% or 50%) can be given intravenously, provided that a plastic catheter delivers the hypertonic fluid into a large vein, due precautions for asepsis being taken. Alcohol given intravenously can also provide a good caloric intake. The average patient has ample fat stores for burning at the rate of 300 grammes per day for ten to fifteen days. Protein should not be given. Testosterone propionate (25 milligrammes per day for ten days at a time) is recommended by some physicians for its effect in slowing protein catabolism.

Examination of the Urine.

Gross hæmaturia may be present during the first week, but it then tends to clear, and so does proteinuria. The specific gravity is between 1·020 and 1·010, normally falling to 1·010. The reaction of the urine is acid. Small numbers of casts may be seen in the urinary deposit, red cells are present, and leucocytes gradually increase in number. Microscopic pyuria is present in nearly all cases, and only diminishes gradually over several weeks.

The Diuretic Phase.

The onset of diuresis does not mean that victory is achieved, for 25% of the deaths caused by acute renal failure occur in the diuretic phase. Initially, the blood urea, creatinine and serum potassium levels may all continue to rise for two or three days, and the patient's general condition may remain poor and even deteriorate. Then there is a rapid fall in the levels of retained products provided an adequate intake of fluid is maintained, and the patient's condition steadily improves, unless extrarenal complications such as sepsis occur.

It is commonly believed that the water and electrolytes lost in the diuretic flood must be replaced by the oral and intravenous routes. This idea is based on the belief that diuresis occurs when renal tubules recover sufficiently to allow of the passage of urine, but that losses may be excessive owing to the osmotic effects of the accumulated solutes now being excreted in large amounts, and to the fact that the tubules have not fully regained their functions. However, there is evidence to suggest that the tubules regain the power of discrimination very early, and that the diuresis is largely the off-loading of excess water and salts which have accumulated during the period of oliguria. Merrill has shown that the diuresis can be controlled by limiting the intake of water and salts as soon as a reasonable bulk of urea and other retained substances has been excreted. In this way the patient may lose five to 10 litres of urine in excess of intake without showing signs of dehydration. It is recommended, therefore, that intake should cautiously be reduced after two or three days of diuresis, a check being kept on the levels of serum electrolytes, till the daily output of urine falls to two or three litres. This output of urine should be maintained during this late diuretic phase for a week or more, since the ability to concentrate may not return to normal for some time. If at any time the serum levels indicate excessive loss or retention of electrolytes, then appropriate adjustments of intake must be made. Caloric intake must be kept up, and within a few days the patient can usually take all food and fluids orally. Protein is included gradually, and as soon as the patient seems well enough he may be allowed to choose his own diet. Complications such as convulsions, urinary tract infections, pneumonia and neurological disturbances may occur. Anæmia may persist for several weeks, and a small transfusion of blood may be indicated, especially if there is delayed healing of wounds. The patient should continue with regular limb and breathing exercises and begin ambulation as soon as possible.

Prognosis.

The mortality rate is 20% to 50% in published cases. Of the patients who survive, most recover adequate renal function. If there is permanent damage, it does not appear to be progressive. The majority of patients will return to health, free of clinical signs and symptoms of renal disease (Lowe, 1952).

Report of a Case.

The patient, aged twenty-eight years, was admitted to this hospital six days after the onset of oliguria which followed Cæsarean section, massive hæmorrhage and an incompatible blood transfusion. Her first six pregnancies had been normal; with the seventh she had an ante-partum hæmorrhage due to *placenta prævia*, and the baby died after being delivered by a classical Cæsarean section. The eighth pregnancy produced a live baby, elective Cæsarean section being performed on rupture of the membranes. The latest pregnancy, her ninth, was uneventful, her blood pressure being about 110 millimetres of mercury, systolic, and 70 millimetres, diastolic,

throughout. At full term she began to lose moderate amounts of blood and clots, and a Cæsarean section was performed with the delivery of a live baby weighing six pounds 14 ounces. There was a low implantation of the placenta.

After the operation the patient continued to lose blood *per vaginam* and was given 500 millilitres of whole blood drawn from the local panel of donors. Her true blood group is O (IV), Rh positive, but it was erroneously regarded as being group A2. The patient had no rigors or shivering, but was otherwise very vague about her immediate post-operative course. Later in the same day she was given a further five bottles of incompatible blood, and she complained of pain in her chest and of difficulty in breathing. The hæmorrhage stopped after four grammes of fibrinogen had been given intravenously, the coagulation time of her blood being reduced thereby from fifteen to four minutes. On the following day she began to vomit continually and was anuric. The intake of fluid was limited to 1500 millilitres daily. Four days after the operation she was given another six bottles of incompatible blood, though most of the fifth bottle was discarded because of the rigor it caused. She later developed an urticarial rash which persisted for several days, and mild jaundice was noticed. During her flight to Sydney she became seriously shocked at 8000 feet, but recovered with oxygen administration, and the aeroplane descended to a lower altitude.

On her admission to Sydney Hospital she was drowsy and confused, felt strange as if floating, and could hear and see people as if they were far away. She had lost all sense of time and was too weak to lift her head. She vomited incessantly, and had a cough which produced a small amount of white mucoid sputum and caused some pain in the region of the right shoulder blade.

On examination, the patient appeared drowsy and jaundiced. The tongue was brown and moist. The abdomen was generally tender, and there was an unhealed lower mid-line wound with a hæmatoma at its upper end and intact sutures. Bowel sounds were present. Both renal angles were tender. The pulse rate was 92 per minute, and the pulse was regular in time and amplitude. The jugular venous pressure did not appear to be raised. The blood pressure was 150 millimetres of mercury, systolic, and 100 millimetres, diastolic. The apex beat was heaving in quality, and was four and a half inches from the mid-line in the fifth left intercostal space. There was a soft, poorly propagated apical systolic murmur, with a systolic murmur in the pulmonary area. The respirations were shallow and numbered 14 per minute, and rhonchi were heard at the base of the left lung. The urine was of small volume, with specific gravity of 1·010. It was acid in reaction and contained clots of blood, a cloud of protein on being boiled, and no sugar.

The provisional diagnosis was acute renal failure due to tubular necrosis following incompatible blood transfusion and hæmorrhage.

Oliguric Phase.

For fifteen days after the onset of the condition the patient passed less than 400 millilitres of urine daily. Initially she was vague, weak and lethargic, unable to speak clearly or to concentrate her attention, and she was unable to lift her head from the pillow even to vomit, which she did frequently. On her admission to this hospital on the sixth day of her illness, the blood urea content was 580 milligrammes per 100 millilitres; the serum sodium content was 135 milliequivalents per litre, the potassium content was 6·9 milliequivalents per litre, the chloride content was 95 milliequivalents per litre and the bicarbonate content was 10 milliequivalents per litre. The hæmoglobin value was 7·5 grammes *per centum*, the hæmatocrit was 21%, and the serum bilirubin content, which had been 1·5 milligrammes per 100 millilitres of blood on the second day of the illness, had increased to 5·0 milligrammes per 100 millilitres. Some of the features of her progress are illustrated in the accompanying graph (Figure I).

On the seventh day she was given three bottles of O (IV), Rh-positive packed cells which had been washed free of serum, an equal volume of blood being removed simultaneously from another vein. Then, on the eleventh day, a polythene catheter was introduced through a saphenous vein into the inferior *vena cava*, 20,000 units of heparin were given, and an exchange transfusion of four litres was carried out. At the same time she was being given a cation exchange resin ("Resonium-A"), 15 grammes four times a day by mouth and by enema. She returned to full consciousness and could remember events clearly from then on. The serum potassium level fell to normal and the resin was suspended. A second exchange transfusion of five litres was given on the twelfth day, followed by a 25% solution of glucose in water given intravenously, two litres daily for three days. Surgical complications occurring during this phase included herniation through the wound of omentum and part of the small bowel on the ninth day; these necessitated resuturing under local anæsthesia.

Diuresis.

On the fifteenth day of the illness the patient's urinary output exceeded one litre, and it increased to 7·0 litres on the nineteenth day. The blood urea level continued to climb during the first two or three days of this phase, as is commonly the case. On the assumption that the urinary flood might be uncontrolled loss by tubules which had not yet regained full function, intravenous infusions were regulated at first to replace the urinary losses of water, sodium and

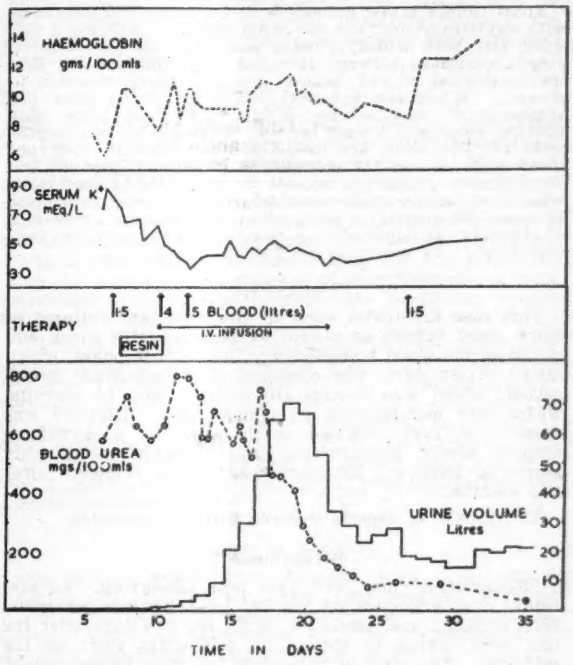

FIGURE I.

The changes in hæmoglobin value, blood urea content and serum potassium level in a case of acute renal failure due to incompatible blood transfusion. Their relation to particular therapy, duration of renal failure and changes in daily urinary volume is shown.

potassium, and to provide additional bicarbonate and calcium. From the fifth day of the regime the intake of fluid was restricted to give one to two litres less each day than the maximum of seven litres, so that the urine flow decreased steadily. However, sodium intake was not reduced correspondingly, and 50 to 100 milliequivalents of potassium were also given daily.

Her blood pressure, which had been steady at 140 millimetres of mercury, systolic, and 90 millimetres, diastolic, during the oliguric phase, began to rise, and on the twenty-second day of the illness, when she had a severe rigor for half an hour, cyanosis for ten minutes and cold extremities, her pulse rate was 180 per minute and her blood pressure 250 millimetres of mercury, systolic, and 180 millimetres, diastolic. Her temperature rose to 102° F. with a similar peak next day. Oxygen was given, but no anticoagulants; the polythene catheter was removed, and the antibiotic "cover" was changed from chloramphenicol, which she had been having throughout her illness, to oxytetracycline. An attempt at blood culture gave a negative result. The episode was thought to have been caused by pyrogens which precipitated a hypertensive crisis, though pulmonary embolism was considered.

Taking fluids orally, she still had some vomiting, and a cumulative fluid deficit of 6·5 litres developed over the next five days, in spite of some thirst but no clinical evidence of dehydration. The blood urea level, which had fallen from 750 to 100 milligrammes per 100 millilitres of blood in seven

days, remained stationary during these five days, and then fell again as the patient increased her oral intake. In the next three days she gained two litres of fluid. By the twenty-sixth day of the illness she had ceased vomiting, her appetite had returned, and she was given a transfusion of three bottles of packed red cells.

Surgical complications during the period of diuresis included rupture of the abdominal wound for the second time, necessitating returning of the bowel and omentum to the abdominal cavity and resuturing of the wound, and infection of the incisions which had been made for introducing the polythene catheters intravenously.

Recovery.

Apart from a breast abscess, which responded to treatment with oxytetracycline, she improved steadily. She ate a full ward diet with added proteins and vitamins, her urinary output continued between 1500 and 3000 millilitres per day, the abdominal wound healed, and the blood returned to normal. When she got out of bed six weeks after her admission to hospital, her weight was eight stone nine pounds, which was normal for her. At follow-up, two months after her admission, she looked and felt perfectly well, her blood pressure was 110 millimetres of mercury, systolic, and 70 millimetres, diastolic, her eye grounds were normal, there was no proteinuria, and her kidneys could concentrate urine to a specific gravity of 1·013. The urea clearance was 80% of standard (43 millilitres per minute) and the urea was concentrated to 2·0 grammes per 100 millilitres.

Discussion.

This case illustrates some of the important features of acute renal failure as caused by post-operative shock and incompatible blood transfusion. The oliguric phase, which lasted fifteen days, was complicated by potassium intoxication, which was successfully treated, and by anæmia, which was not relieved by transfusions. Diuresis was massive at first, and was complicated by a convulsive seizure, severe hypertension, and probably excess body stores of sodium. Recovery was almost complete after two months.

The following aspects deserve further discussion.

"Resonium-A."

"Resonium-A" may well have been life-saving. An oral intake of 60 grammes per day lowered the serum potassium level steadily, and continued to act for two days after the last dose, owing to storage of still-active resin in the intestine. The level of potassium fell even below normal. In general, resins are very variable in their effectiveness, and may be dangerous, for they can release large amounts of ammonium or sodium ions thereby causing acidosis or encouraging the development of pulmonary œdema, and they may remove calcium as well as potassium, with resultant tetany.

Anæmia and Exchange Transfusion.

The three transfusions in the oliguric phase raised the hæmoglobin level only temporarily; it fell to eight grammes per 100 millilitres in a few days. The fourth transfusion of three bottles of packed cells after diuresis raised the level to 13 grammes per 100 millilitres, and the improvement was maintained. The two large exchange transfusions of eight and 10 bottles of fresh blood were probably responsible for the patient's great improvement in state of consciousness, and for the relief of nausea and vomiting. She remembers clearly regaining full consciousness halfway through the first exchange. "Resonium-A" had already produced a fall to normal in the serum potassium level, with improvement in the patient's strength, so that the effect of exchange transfusion on hyperkalæmia could not be judged.

Water and Salt Balance.

In retrospect, it can be seen that this patient, like so many with acute renal failure, was overloaded with water and salt. This was especially apparent during diuresis, and may have contributed to the convulsive seizure. Merrill now advises a net intake of 300 millilitres per day, with no salt at all, during the oliguric phase. Stored blood contains much sodium (from plasma *plus* anticoagulant) and often potassium (from damaged red cells), so that transfusion should be avoided if possible. It is of great advantage if these patients can be weighed daily. If they are bedridden, a special stretcher scale is necessary.

Diuretic Phase.

The massive diuresis was due to an attempt at first to replace fluid lost on the previous day, as the patient had no obvious clinical œdema. A proportion of the sodium and potassium lost was also replaced, probably too much, so that a state of excess salt load was maintained. At first a deficit of two litres in one day was tried, with some reduction in urine volume. Then, after the convulsive seizure, more drastic reductions in fluid and salt intake caused a reduction of urine volume to between two and three litres per day. These observations strengthen the opinion that the diuresis was largely due to excretion of excess water and solutes (urea, creatinine, sodium, potassium, acid radicles *et cetera*) through fairly healthy tubules, and probably not to the indiscriminate loss of necessary body constituents leaking through functionally inefficient tubules.

The Artificial Kidney.

What is the place of an artificial kidney in treating patients such as this one? Clearly, many patients with acute renal failure recover when carefully treated conservatively; but a good deal of support is forthcoming from different centres for the use of an artificial kidney in selected cases (Alwall, 1947; Merrill, 1955; Elkinton and Danowski, 1955). It is held that mortality is reduced, complications are fewer and the mental and physical condition of patients can be improved quite remarkably. Dique (1955) reported the first use of this form of treatment in Australia. It stands to reason, of course, that removal of toxic substances is the ideal method of treatment, rather than the addition of palliative or neutralizing agents. Dialysis offers the most efficient means, and extracorporeal dialysis in an artificial kidney is preferable to gastric or intestinal irrigation or peritoneal dialysis, which is less efficient and more hazardous. Hæmodialysis in an artificial kidney is the method of choice for correcting the biochemical disorders of the extracellular fluid, the most dangerous of which is hyperkalæmia. Also coma or stupor, carrying with it the dangers of bronchopneumonia and thromboembolism, can often be completely relieved. Nausea and vomiting, which may be exceedingly distressing, are also frequently relieved. Glucose can be made to diffuse in the opposite direction, from the artificial kidney into the patient's plasma; this gives added calories and helps to spare excessive protein catabolism. Water can also be removed by ultrafiltration when the patient has been overhydrated and is suffering from cardiac failure or pulmonary œdema during the period of oliguria. Thus dialysis may prove invaluable, used as an adjunct to skilled conservative management.

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For permission to report this case I am grateful to Dr. J. N. Sevier, the physician in charge, and to Dr. Norman Rose, the Medical Superintendent of Sydney Hospital. Valuable help in management was given by Dr. G. A. W. Johnston and Dr. H. S. H. Wardlaw, of the Kanematsu Institute, and by Dr. R. J. Walsh, of the Red Cross Blood Transfusion Service. Dr. H. M. Whyte helped in preparing this article.

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DIETARY FIBRE AND TOXÆMIA OF PREGNANCY.

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THE influence of dietary habits on the incidence of toxæmia of pregnancy has been noted by many investigators. However, the factor or factors in the diet which predispose the subject to or protect her from toxæmia are still controversial.

Hipsley (1953) reviewed the literature on the subject and showed that many of the previous conflicting observations could be reconciled if the fibre content of the diet was considered. He suggested that an increased fibre content in the diet (or factors associated with the fibre) tended to prevent toxæmia, and this explained why populations with a so-called "poor" diet of high fibre content (either by racial habits, or by force of circumstances) were less prone to toxæmia of pregnancy.

Objects.

In order to study further the hypothesis put forward by Hipsley, it was decided to conduct a dietary survey of pregnancy toxæmia patients admitted to the Royal Hobart Hospital over a given period, and to compare the fibre content of their usual diet with that of a control group of pre-confinement and post-confinement patients without toxæmia admitted to the hospital over the same period.

Material.

The period of the study extended from September 15, 1955, to September 15, 1956.

All patients admitted to hospital over this period with the diagnosis of preeclamptic toxæmia were interviewed by one of us (J.F.H.), and a history of the normal diet of each patient was obtained; this was the "toxæmic group". An equal number of unselected but non-toxæmic pre-confinement and post-confinement patients admitted to hospital over the same period were similarly interviewed and the same dietary data were collected; this was the "control group". The fibre content of the diet of each patient was then calculated by means of fibre tables of the fifth report of the Advisory Council on Nutrition (1938). The fibre contents of the diets of the two groups were then compared, and the results were submitted to statistical evaluation.

Criteria for Inclusion in the Toxæmic Group.

The standards taken for admission of toxæmic patients to this hospital are as follows: (i) a resting blood pressure of 140 millimetres of mercury, systolic, and 90 millimetres, diastolic, or more, and/or (ii) albumin in a catheter specimen or urine, with the exclusion of those patients microscopic examination of whose urine reveals significant pus cells, and/or (iii) pitting œdema to the knee (in the absence of local causes), and/or (iv) a weight gain of over one pound per week after the twenty-eighth week, not controlled by rest, diet and sedation at home. All the toxæmic group fell into one or other (usually at least two) of these categories.

Patients admitted to hospital were chosen for the following reasons: (i) The foregoing criteria could be rigidly applied, and therefore no patient falling into the "toxæmic" group would be missed in the dietary survey. (ii) There are extreme practical difficulties in attempting to obtain adequate and accurate dietary histories during the visit of a patient to the busy ante-natal clinic. The difficulties become practically insurmountable when only one nutrition officer is available for such a study. An attempt to solve the problem by having several observers compile the histories introduces obvious fallacies, and this idea was therefore discarded.

Criticisms.

For administrative reasons, it was impossible to arrange the patients so that the nutrition officer interviewing them (J.F.H.) had no knowledge of the group to which each patient belonged. This admittedly introduces the element of possible personal bias; but as the object of this study was not to substantiate the work of Hipsley but rather to test its validity, it is thought that this element is minimal. Further, when the fibre content of each diet was calculated from the charts, the calculations were carried out without knowledge of the groups to which the particular patient belonged.

The dietary surveys were carried out during the patients' stay in hospital, and as this was usually during the third trimester (or after delivery) there was a definite interval between the time when the diets were being consumed and the time of the survey. This introduces the possibility of some inaccuracy; but Woodhill (1952) considers that this is largely avoided provided that the dietary history extends over a reasonably long period. The latter precaution was observed in these cases.

Rejection of Subjects.

One patient admitted to hospital with preeclamptic toxæmia was excluded from the study because language difficulty prevented the elucidation of a reasonably accurate dietary history, in accordance with the recommendation of Smith and Stuart (1948). Fortunately, the nutrition officer (J.F.H.) was linguistically capable of dealing with all patients speaking German, Dutch or English, and this explains the small number excluded because of language difficulty. It would appear that the command of several languages is a highly desirable quality in workers conducting such surveys in Australia at the present time, in order to obtain a representative sample of patients (Woodhill, 1952).

Seven patients who had a proven history of essential hypertension, or whose blood pressure on a visit to the ante-natal clinic before the twenty-fourth week exceeded 140 millimetres of mercury, systolic, and 90 millimetres, diastolic (Greenhill, 1951), were excluded from the study. This was done because all patients with essential hypertension are admitted to hospital as a routine (for full medical investigation and assessment) at their first visit to the ante-natal clinic. Thus they would fall into the "toxæmic" group above (according to our criteria) whether they had really developed true superadded toxæmia or not. Again, the lability of the blood pressure in many such patients and the varying level from patient to patient make it difficult to lay down definite and fixed criteria beyond which preeclamptic toxæmia may be said to be present—for the purposes of a survey of this kind. Therefore, as these patients could clearly produce misleading results—and, moreover, results dependent largely on personal interpretation (or misinterpretation)—they were excluded.

Unbooked patients (of whom there were only a small number) were included in the toxæmic group only after confirmation from their attending doctor that they had been normal at the beginning of pregnancy. One patient was excluded on these grounds.

Results.

Age.

The average age in the "toxæmic" group was twenty-five years ten months, the youngest patient being aged seventeen years and the oldest forty-six years. Comparable figures in the control group were twenty-five years ten months, eighteen years and forty-three years (Table I).

Number of Pregnancies.

The average number of previous pregnancies with viability of the fœtus (that is, beyond the twenty-eighth week) in the toxæmic group was 1·2, compared with 1·8 in the control group. The maximum number of such pregnancies in the "toxæmic" group was eight, and in the control group six.

Signs of Preeclamptic Toxæmia.

The incidence of the criteria set down for the diagnosis of preeclamptic toxæmia is set out in Table II. It will be observed that 52 patients (75%) showed œdema, 54 (78%) excessive weight gain, 52 (75%) hypertension and 17 (24%) albuminuria.

The vast majority of the patients, of course, had more than one of the criteria present.

Fibre Content.

The average fibre content of the diet of the toxæmic group was 4·8 grammes, the maximum being 12·6 grammes and the minimum 1·5 grammes.

The average in the control group was 6·92 grammes, the maximum being 18·17 grammes and the minimum 3·36 grammes.

A *t* test indicated that the difference between these averages was very highly significant ($t = 4·52$—136 degrees of freedom). The significance level was 0·1% (Table III).

Discussion.

It has been pointed out (Hipsley, 1953) that in those native races who consume a diet rich in fibre, the incidence of preeclamptic toxæmia is extremely low and eclampsia is practically unknown. Races who have undergone dietary surveys with results supporting the foregoing contention include the Fijians (Bell and Wills, 1950), New Guinea natives (Hipsley, 1949), Celebes Islanders (De Wijn, 1952), Javanese (De Haas, 1952), Belgian Congo natives (Salzmann, 1956), and the Transkei natives (Crichton, 1947).

It is also well known that in those civilized population groups who, because of privations of war, were forced to consume large quantities of foods such as turnips, potatoes, sugar beet, bulbs, *et cetera*, in place of "civilized" carbohydrate-rich foods, the incidence of preeclampsia and eclampsia fell to extremely low figures. This was the case in Germany (1914-1918), the Netherlands (1940-1945) and Mastboom (1948). Again, it is clear that these people were consuming a diet necessarily high in fibre content. At the opposite extreme, many population groups with diets low in fibre content have been shown to have a very high incidence of toxæmia of pregnancy—for example, many parts of India (Mudaliar, 1938), Ceylon (Theobald, 1946), the Indians living in Fiji (Bell and Wills, 1950), and Hong Kong in the period 1940-1941 (King and Ride, 1945).

It is not intended to review this literature in detail, as this has already been comprehensively done by Hipsley (1953), and the reader is referred to this monograph for a detailed consideration of the above-mentioned papers. However, it is interesting to consider recent surveys of the effects of planned alteration in the diet of pregnant women in civilized communities, in the light of the foregoing facts.

Planned Changes in Diet during Pregnancy.

Duncan, Baird and Thompson (1952) showed that in Scotland, from 1943 onward, there was a steady fall in the still-birth rate due to toxæmia; this they attributed to improved economic conditions (including scientific rationing) rather than to improved ante-natal care. One important change in the diet was that in bread from 72% extraction to 85% extraction (in 1942). Hipsley has pointed out that this would increase the fibre content of the average diet from approximately 1·2 to 2·4 grammes per 1000 Calories.

It is an interesting coincidence that if an average diet of 2700 Calories was taken, this would mean a fibre content of 3·24 grammes (before 1942) compared with 6·48 grammes (after 1942), these figures having a similar relationship as those of our "toxæmic" and "control" groups (4·8 grammes and 6·92 grammes). (An average diet of 2700 Calories is taken as the recommended amount of Calories for a woman aged twenty-five years during the third trimester of pregnancy—National Health and Medical Research Council recommended daily dietary allowances, 1953.)

Hamlin (1952) reported the results of a planned attack on preeclampsia and eclampsia at the Women's Hospital, Crown Street, Sydney. Great stress was laid on dietary control, patients being given a diet of low carbohydrate, high protein and high vitamin content before mid-pregnancy. Dietary measures were coupled with very strict ante-natal supervision. This dietary regime would have the effect of increasing the fibre intake, as high-calorie carbohydrates are replaced by more bulky (and fibrous) lower-calorie fruits and vegetables. Eclampsia was virtually eliminated by this planned attack.

Nixon (1955) states that similar dietary measures to those of Hamlin are being used at University College Hospital, London, to attempt to diminish the incidence of toxæmia, but he does not outline the results of the measures to date.

"Poor" Diets and Pregnancy Toxæmia.

A survey of the literature reveals many studies of the influence of the "poor" civilized diet (as distinct from the so-called "poor" native diet) on the incidence of toxæmia of pregnancy.

Also of interest are the findings of Dieckmann *et alii* (1952), who studied the weight gain of toxæmic and hypertensive patients from the early weeks of pregnancy, and showed that excessive gain in weight began as early as the thirteenth week in patients who subsequently developed signs of toxæmia. They stated that "these data furnish important evidence that pre-eclampsia and eclampsia is not a fulminating condition in the last trimester of pregnancy, but that the onset began months before the clinical condition became evident as either pre-eclampsia or eclampsia". In other words, an *ætiological factor* (or factors) of long standing is of paramount importance in these cases.

The studies of Woodhill (1952, 1955), of Theobald (1955), of the Committee of Inquiry into the decline of the birth rate (1948) and of others have shown conclusively that

TABLE I.

Group.	Number of Patients.	Age (Years).			Number of Pregnancies.	
		Average.	Maximum.	Minimum.	Average.	Maximum.
Toxæmic ..	69	25 10/12	46	17	1·2	8
Control	69	25 10/12	43	18	1·8	6

those pregnant patients with a "poor" civilized diet are more prone to toxæmia of pregnancy. However, we have been unable to find any previous controlled study of the differences in fibre content of the diet of patients with toxæmia and those without toxæmia. From the results obtained in our study, and the racial variation in incidence of toxæmia (apparently it varies inversely with the dietary fibre content of the diet), it seems clear that this aspect of the problem is worthy of further study.

TABLE II.

Criterion of Toxæmia.	Number of Patients.
Weight gain	54 (78%)
Raised blood pressure ..	52 (75%)
Œdema	52 (75%)
Albuminuria	17 (24%)

It would be particularly interesting to investigate whether it is the dietary fibre itself, or rather a factor (or factors) constantly associated with it, which provides the "protection" from toxæmia.

Conclusions.

1. From a survey of the literature, it would appear that the great variation in incidence of toxæmia of pregnancy from race to race and from period to period bears a close relationship to the varying percentage of fibre in the diet, the incidence of preeclampsia and eclampsia varying inversely as the percentage of dietary fibre.

TABLE III.

Group.	Dietary Fibre Content (Grammes).		
	Maximum.	Minimum.	Average.
Toxæmic	12·6	1·56	4·8
Control	18·17	3·36	6·92

2. It is probable that a factor (or factors) of paramount importance in the development of pregnancy toxæmia acts for a considerable period (several months) before blatant clinical signs of toxæmia appear.

3. Scientific alteration of the diet of pregnant women which has the effect of increasing the dietary fibre has been shown to diminish considerably the incidence of toxæmia of pregnancy.

4. A survey of the normal diets of a group of patients with pregnancy toxæmia revealed that their diets were very significantly lower in fibre than were those of a control group.

Summary.

1. A survey of the usual diet of patients admitted to the obstetric ward of the Royal Hobart Hospital with pre-eclampsia and eclampsia was carried out, and a comparison was made with the usual diet of a control group of non-toxæmic patients admitted to the obstetric ward over the same period.

2. The average amount of fibre in the diet of the toxæmic group was 4·8 grammes, compared with 6·92 grammes in the control group. This difference is significant at the 0·1% level.

3. It is considered that this aspect of the influence of diet on the incidence of toxæmia of pregnancy is worthy of further study.

Acknowledgements.

We wish to thank the honorary obstetricians of the Royal Hobart Hospital and the general superintendent, Dr. J. M. M. Drew, for permission to interview the patients and for advice and assistance. Our thanks are also due to Sister F. I. Taylor and Sister E. V. Worbey, of the Royal Hobart Hospital, for their continued interest and assistance in this study, and to Mr. P. Sprent, of the University of Tasmania, who assisted in the planning of the study and carried out the statistical evaluation of the results.

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Reviews.

The Practice of Psychosomatic Medicine: As Illustrated in Allergy. By Hyman Miller, M.D., and Dorothy W. Baruch, Ph.D.; 1956. New York, London, Toronto: McGraw-Hill Book Company, Incorporated. 9" × 6", pp. 207. Price: $5.00.

WRITTEN by a physician and a consulting psychologist, this enjoyable book presents in a simple but comprehensive form the authors' views on the ætiology, mechanisms and treatment of allergic conditions.

While consideration of constitutional, infective and immunological factors is quite properly included, the major part of the book deals with the effect of emotional defects, dissatisfactions and disturbances upon individuals whose physiological reactions appear as signs or symptoms of one allergic state or another. In a controlled study, Miller and Baruch found that: "In the allergic sample, there was verbal evidence from the mothers showing that 97% of the children had been living in an emotional climate where maternal rejection prevailed." In non-allergic controls, 36·7% were seen to have been rejected—these were children with a variety of behaviour problems.

Mechanisms in the production of symptoms are described at some length and in modified psychoanalytical terms. However, readers who find psychoanalytic theory to be unacceptable or unfamiliar will still find much of interest and value in other sections.

Of course, there is nothing new in the information that disturbed feelings can be largely responsible for allergies or many other illnesses. Also, it is widely agreed that unsatisfactory child-parent relationships result in many

common forms of bodily and personality disorders. However, perhaps the most helpful part of this book is the advice on management and treatment, a topic which a great many writers in this field find difficulty in reducing to terms which the average physician can understand and employ. As so few of the thousands with psychosomatic conditions can secure long and complex psychotherapy, it is encouraging and stimulating to find an extremely simple and (the authors claim) most effective plan for helping people to overcome their pathogenic emotional problems.

Apart from an explanation of the authors' basic therapeutic technique, further advice is given on such important matters as handling the patient's parents, the attitudes of nurse and technician to the patient, and even dealing with the patient's worry over his fees.

For the practical advice it offers on the solution of many human problems, this book deserves to be read widely. As a contribution to medical literature, it ranks with such work as Alvarez's "Nervousness, Indigestion and Pain".

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P.; Fifth Edition; 1956. Edinburgh and London: E. and S. Livingstone, Limited. 8¾" × 5¾", pp. 696, with 155 illustrations, 12 in colour. Price: 37s. 6d.

FROM time to time, every doctor is faced with some emergency with which he is not wholly familiar. In this volume Dr. C. Allan Birch and his collaborators describe every possible medical emergency and detail the necessary therapeutic measures. For the purpose of the work, medical emergencies are defined as all emergencies except those requiring surgery. The authors of chapters on the various specialities are all acknowledged experts in their respective fields, which makes their advice authoritative. Emergencies at sea, in the air and in the tropics are dealt with, and so, too, are such topics as emergencies arising from practical procedures, from anæsthesia and from drug side-effects, to mention only a few. Modern methods of artificial respiration are described and illustrated with an excellent series of photographs, and the practical details given for resuscitation in a rowing-boat or up a lamp-pole are novel but valuable.

The work is most comprehensive, and the recognition of its worth can be seen by the fact that it has appeared in German and Spanish editions—surely a rare distinction for a British medical tome. It is an asset that all practising doctors should have for handy reference.

Anatomy for Surgeons: The Thorax, Abdomen and Pelvis. By W. Henry Hollinshead, Ph.D.; Volume II; 1956. New York: Paul B. Hoeber, Incorporated. 10½" × 7¼", pp. 952, with 1109 illustrations. Price: $20.00.

THIS is the second volume of a regional anatomy, which is an attempt to describe and interpret the anatomical facts and concepts which are of particular importance to the surgeon. It is based on the author's experience of over a quarter of a century as a teacher of anatomy to medical undergraduates, and to post-graduate classes of Fellows of the Mayo Foundation specializing in various branches of surgery. Every chapter has been criticized by one or more surgeons, whose work keeps them in constant touch with the particular anatomy described. Every attempt has been made to gather together pertinent material from all available sources, including embryology, neuroanatomy, and variations and anomalies, as well as experimental work, a knowledge of which is essential for complete understanding. The text is profusely illustrated with half-tone illustrations and diagrams, both original and modifications of well-known figures, which greatly help in following the text. This work, when completed, will be one of the most useful and instructive texts of its kind that has appeared up to the present time.

Orthopædic Nursing. By Mary Powell, S.R.N., M.C.S.P., with a foreword by Sir Reginald Watson-Jones, B.Sc., M.Ch.Orth., F.R.C.S., F.R.C.S.E. (Hon.), F.R.A.C.S.(Hon.), F.A.C.S.(Hon.); Second Edition; 1956. Edinburgh and London: E. and S. Livingstone, Limited. 8¾" × 5¾", pp. 451, with illustrations. Price: 27s. 6d.

ONE of the main changes noticed in the second edition of "Orthopædic Nursing" by Matron Mary Powell is in reference to tuberculosis, the therapy of this disease having been revolutionized by the discovery of streptomycin, para-aminosalicylic acid and isonicotinic acid. However, the general principles for nursing patients with tuberculous lesions of bones and joints are still the same; but the time period for recovery is greatly shortened and the risk of complications is much less.

All aspects of orthopædic nursing are covered fully, and special emphasis is placed upon the care of patients wearing splints and plaster casts. Full details for the correct application of all types of plaster casts are given, 29 pages being devoted to this subject and 32 pages to splints and appliances, while many photographs greatly enhance the written text. The nursing of patients with all diseases of the musculo-skeletal system is detailed, whether these are of congenital or acquired origin, and the completeness of the chapter on poliomyelitis is worthy of special mention.

Following as it does in the tradition of the Liverpool School of Orthopædics and of its mentor, Sir Robert Jones, this book is a worthy memorial to the nurse who helped him, Dame Agnes Hunt, to whose memory the volume is dedicated. All nurses working in orthopædic wards will find this work an invaluable guide at all times. It is another high-class production of the standard now expected of the House of Livingstone.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"The Medical Clinics of North America: Chicago Number: January, 1957: The Sick Heart", edited by Wright Adams, M.D., and Fausto Tanzi, M.D.; 1957. Philadelphia and London: W. B. Saunders Company. 9" × 5¾", pp. 302, with 51 figures. Price: Cloth binding, £8 2s. 6d. *per annum*; paper binding, £6 15s. *per annum*.

Contains 20 articles on heart disease planned primarily for the physician in active practice. Most of the articles are concerned with diagnosis and treatment, but other aspects are included.

"The Physiology of Gastric Digestion", by A. H. James, D.M. (Oxon.), M.D. (Toronto), B.Ch., M.R.C.P.; 1957. London: Edward Arnold (Publishers), Limited. 8½" × 5½", pp. 204, with 54 illustrations. Price: 28s.

The approach is that of the clinician.

"Cleft Lip and Palate", by W. G. Holdsworth, F.R.C.S. (Edin.), F.R.C.S. (Eng.); Second Edition; 1957. London: William Heinemann (Medical Books), Limited. 9¾" × 7¼", pp. 200, with 146 illustrations. Price: 42s.

Some of the book has been rewritten and additional material includes a chapter on the embryology, development and growth of the face by Professor Richard Harrison.

"The Cytology of Effusions in the Pleural, Pericardial and Peritoneal Cavities", by A. I. Spriggs, D.M. (Oxon.), M.R.C.P.; 1957. London: William Heinemann (Medical Books), Limited. 9¾" × 7¼", pp. 80, with 40 illustrations. Price: 42s.

Intended for use along with the standard hæmatological atlases to help in the identification of cells in the fluids named.

"Blood Pressure Sounds and Their Meanings", by John Erskine Malcolm, B.Sc., M.B., Ch.B., F.R.C.S.; 1957. London: William Heinemann (Medical Books), Limited. 7¼" × 4¾", pp. 104, with 45 illustrations. Price: 12s. 6d.

The author offers an explanation of the nature and origin of Korotkov's sounds.

"A Textbook on the Nursing and Diseases of Sick Children: For Nurses", by various authors, edited by Alan Moncrieff, C.B.E., M.D., F.R.C.P., J.P., and A. P. Norman, M.D., F.R.C.P.; Sixth Edition; 1957. London: H. K. Lewis and Company, Limited. 8½" × 5½", pp. 793, with 146 illustrations. Price: 50s.

Completely revised and rearranged since publication of the previous edition in 1952.

"The Eye: In General Practice", by C. R. S. Jackson, M.A., B.M., B.Ch. (Oxon.), D.O.M.S., F.R.C.S. (Edin.); 1957. Edinburgh and London: E. and S. Livingstone, Limited. 8½" × 5½", pp. 160, with 25 illustrations. Price: 21s.

Written for general practitioners by an ophthalmologist who has been a general practitioner.

The Medical Journal of Australia

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All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

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THE GOOD LIFE.

THERE comes a time in the lives of most of us when, with different degrees of intensity and honesty, we obey the Socratic exhortation "Know thyself". It is certainly well that we should ask ourselves what are the dominant motives and aims in our modes of living. Do we seek a better way of life, or do we strive merely towards getting a better living? Charles W. Morris, Lecturer in Philosophy in the University of Chicago, has for some years been engaged in research into human values. In earlier studies he postulated three basic components of human personality and chose descriptive terms for them: dionysian, displaying tendencies to release and to indulge existing desires; promethean, displaying tendencies to manipulate and remake the world; buddhistic, displaying tendencies in the self to regulate itself by holding in check its desires. Individuals differ in the relative strength of these components, and the differences are reflected in various cultures, religions, ethical systems and philosophies, and also in art forms. More recently Morris[1] has set out to determine what are man's preferences for ways of living, which may vary from the "good time" kind of life to modes of conduct which conform to high ethical standards. To this end he formulated 13 "ways of life", each described in about a hundred words and summarized in such terms as "Way 1—Preserve the best that man has attained"; "Way 5—Act and enjoy life through group participation"; "Way 10—Control the self stoically"; "Way 13—Obey the cosmic processes". Students in universities in the United States of America, India, China, Europe and Australasia were invited to express their preferences by rating each of the 13 ways according to a scale from 7 ("I like it very much") to 1 ("I dislike it very much"). Some 3000 men and 1500 women completed the *questionnaire*; the majority were in the United States, over 1000 were in India, and 700 were in several universities in China. Australia was one of several countries which did not respond to the invitation. Many of the American students were interviewed after completing the ratings, and various personal details, including temperament, physical characteristics according to Sheldon's categories, religious affiliations and economic status were noted. The replies to the *questionnaire* were subjected to a factor analysis, in order to determine the smallest number of dimensions which would account for the intercorrelations among a number of variables. From this analysis there emerge five main factors with the following characteristics: (*a*) Social restraint and self-control; appreciation and conservation of what man has attained. (*b*) Enjoyment and progress in action; emphasis on initiation of change with delight in vigorous action. (*c*) Withdrawal and self-sufficiency; focus on self, on rich inner life, high level of insight, but not self-indulgence. (*d*) Receptivity and sympathetic concern; responsiveness to external stimuli for inspiration. (*e*) Self-indulgence and sensuous enjoyment, either in simple pleasures or in abandonment to the moment.

Morris points out some of the implications and limitations of his research into human values. The word "value" may be used in different senses. It may imply a mere preference for an ideal with little or no impact upon behaviour. As an example, the drug addict may quite firmly believe that it is better to abstain. Such a "conceived" value is to be distinguished from an "operative" value, which determines a course of action. In yet another sense the term "value" may be concerned with what is preferable or desirable, whether or not it is conceived or acted upon as preferable. The diabetic, having received advice about his diet, may have his preferences for certain foods, which may or may not be on the prescribed list. The diabetic who prefers to live rather than to die has to exercise what Morris terms "object" values, since the stress in this instance lies on the properties of objects (articles of diet). In his study of "ways to live" Morris is concerned primarily with conceived values, with a study of conceptions of the good life. The size and consistency of the American sample, and the fact that the replies to the *questionnaire* were voluntary and unsigned, were indications of the reliability and worthwhileness of the investigation, even though the profession of preferences gave no indication of how the students actually lived or whether they would really like to live according to their conceived values. As St. Paul said, following Ovid: "For the good that I would I do not: but the evil that I would not, that I do." By reason of various internal and external influences some ways are more difficult to follow for some persons than for others, and the social system in which a person is brought up clearly is a powerful determinant of preferences and of ways actually lived. Conceived values effect a compromise

[1] "Varieties of Human Value", by Charles Morris; 1956. Chicago: The University of Chicago Press. 9¼" × 6", pp. 225, with illustrations and tables. Price: $5.00.

on the intellectual plane between personal inclinations and drives and social requirements. True satisfaction and inner harmony will more surely be attained in so far as conceived values are actually given expression in conduct.

However, Morris's work is an experiment in mensuration, not in moralizing. He is satisfied that he has found a cross-cultural interval scale for measuring values, that five value dimensions appear in the three main cultural samples (from the United States of America, India and China), and that he has accumulated sufficient evidence to support a field conception of values. The five value dimensions, which are characterized as social restraint and self-control, enjoyment and progress in action, withdrawal and self-sufficiency, receptivity and sympathetic concern, and self-indulgence or self-enjoyment, and which appear to be basic and in various proportions components of conceptions of the good life in diverse cultures, may be compared with a hypothetical use of five major tones in the composition of different melodies. Not unexpectedly the rating scores varied with differences in sex, temperament, character, somatotype, economic status, size of the communities in which the students were raised and intracultural traditions; variations within a culture were less than those between different cultures. Psychological and constitutional characteristics showed the closest relation to ratings of the ways, sex and body-size the least, with population variations and economic status in between.

Coming now to the broad conclusions of the research, we find that American students in general gave a high rating for Way 7—"dynamic integration of enjoyment, action and contemplation". They displayed more orientation to self than other national groups, laid more emphasis on personal possessions and showed a weaker inclination to society. Indians preferred Way 1—"balance, moderation, understanding participation in society, respect for human culture and gradual social change". In their comments the Indian students referred to the problem of reconciling tradition with reconstruction, inwardness with outer activity. Chinese students in universities in four Provinces agreed in preferring enjoyment and progress in action, with high ratings for withdrawal and self-sufficiency and least stress on service to fellow-men. The Japanese answers indicated orientation to persons and to society, and respect for inwardness as amongst the Indian samples, but with greater receptivity to nature. Norwegian students showed strong religious trends, greater sensitivity to conscience, more orientation towards society and the cosmos than to self, and low emphasis on self-indulgence, possessiveness or desire for power for its own sake. It may be noted that Norway has one of the highest suicide rates. Samples from other participating countries were too few to be of statistical value.

This research was carried out on somewhat narrowly selected subjects—namely, students, most of whom were in the faculties of arts or philosophy, with a few in the sciences and medicine. The preferences expressed by these young people may change by the time they reach a mature age. One might expect that inclination towards a career as an engineer, a physicist or a physician might be reflected in a choice of "ways". The way of life of a mature physician was expounded in an address to the students of Yale University in 1913 by Sir William Osler.[1] His way was based on some words of Carlyle which had influenced him since his own student days: "Our main business is not to see what lies dimly at a distance, but to do what lies clearly at hand." He went on to say that on a basis of a well-trained and disciplined body, the student who diligently acquired the habit of a well-directed mind, able to concentrate intensely on the task before him, had little to fear for his future. Moreover, such a habit of mind provided a sound foundation for a sane outlook on life. Osler also advised his hearers to round off each day with a few minutes spent with the writings of the great minds. In this delightful and inspiring address, in which he gave of the best of his culture and experience, Osler pointed out a way most pertinent for our profession if it would know something of "the good life".

Current Comment.

CARBON DIOXIDE INTOXICATION.

A SYNDROME, which has been called carbon dioxide intoxication, has been recognized since about 1930, and much has been written about it. This condition can occur in persons with disorders which greatly reduce alveolar ventilation. Symptoms and signs vary considerably between patients and may simulate other diseases. H. O. Sieker and J. B. Hickam[2] have studied the syndrome in great detail in 25 cases seen by them during the last five years. Most of the patients had chronic pulmonary disease, such as obstructive emphysema, asthma alone or with some other pulmonary condition, tuberculosis and carcinoma of the lung. Three patients showed no evidence during life or at autopsy of pulmonary disease. In order to establish the diagnosis, arterial blood oxygen saturation, pH and carbon dioxide tension were determined. The arterial blood carbon dioxide tension was in all cases high, but it reached extremely high levels when the patient was breathing high concentrations of oxygen.

The primary symptoms and findings in cases of carbon dioxide intoxication are those of a neurological disorder. Headaches, somnolence and mental confusion are common; and as the intoxication progresses, the patient develops weakness, lassitude, irritability, increasing mental confusion and drowsiness. Finally a variety of symptoms and coma usher in death. If carbon dioxide is administered to a normal person, it produces unconsciousness and depresses respiration if in sufficient concentration. The general symptoms shown in the syndrome are also produced by inhalation of certain concentrations of carbon dioxide. Apart from the general symptoms mentioned, patients with carbon dioxide intoxication show a variety of symptoms associated with the central nervous system. There is great variation in the concentration of carbon dioxide in the blood and also in the mental state. The arterial blood carbon dioxide tension was as high as 127 millimetres of mercury and the pH as low as 7·16 in a patient who was still conscious and responsive. The comatose state was observed in patients with an arterial blood carbon dioxide tension ranging from 91 to 228 millimetres of mercury and a pH of 7·25 to 6·86. Generally, as the carbon dioxide tension of the blood increased, the mental state changed from consciousness to coma.

Sieker and Hickam point out that a change in the mental state of a patient with impairment of alveolar ventilation should lead to a suspicion of the diagnosis of carbon dioxide intoxication. Diagnosis is made ultimately by analysis of an arterial blood sample for carbon dioxide tension and pH. Prevention is important, and this can result only from correction of the factors which cause the

[1] "A Way of Life", by William Osler; 1937. New York: Paul B. Hoeber, Incorporated.
[2] *Medicine*, December, 1956.

retention of carbon dioxide. Of the 25 patients in this series 23 were comatose on one or more occasions. Therapy for the first 13 patients seen was with bronchodilator drugs, bronchoscopic drainage, expectorants and antibiotics and nasal administration of oxygen. For the last 12 patients, in addition to these measures, mechanical respirators were used. Sieker and Hickam state that good results were obtained with the mechanical respirators, but inspection of their tables shows that of the first 13 patients seven died, while of the last 12 patients six died. The use of oxygen therapy seemed indicated for several patients, but the effect of this was to cause greater retention of carbon dioxide in some of the patients. It would seem that the syndrome is not uncommon, that prevention is important, and that if the condition does occur the earliest possible treatment is advisable.

THE "PERMEABILITY" HYPOTHESIS OF THE ACTION OF INSULIN.

SINCE insulin was discovered thirty-five years ago there has been a great deal of discussion about how and where the hormone acts in the lowering of blood sugar concentration. So far there is no hypothesis which is generally acceptable. One of the difficulties is that the molecule of insulin is of large size, has a high molecular weight and, one would expect, would pass through a cell membrane with great difficulty if at all. E. J. Ross[1] suggests that insulin accelerates the transport of glucose and some other sugar across the cell membrane, and that this represents the principal locus of insulin action; he adduces evidence at great length to support this hypothesis.

The cell membrane of animal cells consists largely of lipoids, and the rate of penetration of solutes from the outside to the interior of the cells depends on the lipoid solubility of the solutes except in the case of glucose and some other sugars. Thus sucrose has a partition coefficient between ether and water nearly the same as that of glucose, yet sucrose enters cells very slowly while glucose enters readily in the presence of insulin. Other sugars which show the same rate of absorption into cells as glucose (or a faster rate) are D-glucose, D-galactose, D-xylose and L-arabinose, all of which have the same configuration on the first three carbon atoms. Not all cells require the presence of insulin to enable them to take up glucose readily. Ross quotes considerable evidence to show that liver cells do not need insulin to facilitate glucose absorption. An hypothesis which has been widely accepted is that insulin activates the hexokinase enzyme system within cells in the conversion of glucose to glucose-6-phosphate, but evidence is now strongly against this proposal. Since the rate at which glucose penetrates cell membranes is much greater than would be expected from its solubility in the lipoid phase of the cell membrane, it is evident that some form of "activated" or "facilitated" transport of glucose across the membrane exists. For absorption of glucose across the intestinal mucosa and across the cells of the renal tubules, which is not affected by insulin, there is considerable evidence that energy is used in an enzyme system involving phosphorylation of the glucose. Similar conditions hold for the absorption of glucose by red corpuscles. Not everyone, however, accepts this idea.

In the case of muscle cells there is little evidence that there is an increase in the absorption of phosphate ion when glucose is being absorbed under the action of insulin. Indeed, the absorption of glucose is greater from a bicarbonate medium than from a phosphate medium. Galactose, L-arabinose and D-xylose are not phosphorylated by muscle kinases, although they are easily absorbed by muscle cells. These and other considerations lead to the belief that entirely different mechanisms are responsible for the entry into muscle cells and into intestinal mucosa, renal tubules, red corpuscles and hepatic cells. Ross's suggestion is that insulin couples with monosaccharides of a certain configuration and enters a carrier system whose transport is accelerated by insulin in the case of muscle cells. The carrier may be an enzyme system-glucose transferase.

Birds show great variation in their response to insulin. Cold-blooded invertebrates are resistant to insulin. It is suggested "that the development of a specialised system for the transport of glucose into muscle cells is an adaptation advantageous to the evolution of higher forms, and that the additional acceleration of the transport mechanism by a circulating hormone, insulin, is a further development to meet sudden environmental stresses".

[1] *Medicine*, December, 1956.

POLLEN FALLOUT.

THE spring and summer prevalence of pollens is well known, and many a sufferer from hay fever and asthma knows the hazard of a country excursion. For the sufferer the city is a place of security and safety, at least so far as pollens are concerned. The movement of pollen and moulds in the atmosphere has, of course, been studied fairly extensively, and it is generally held that the rate of temperature change with altitude is the most important factor regulating the rise and fall. These particles are held in currents which tend to rise vertically so long as air cools with increasing altitude—that is, where the temperature lapse rate is high and the air consequently unstable. The particles are carried to a level where increasing altitude is no longer accompanied by a temperature drop. This is usually a cloud layer or a haze layer. The particles therefore tend to concentrate at this level. The rate at which the pollen and mould particles fall out is related to the time of day. During the night and in particular towards early morning, the radiation from the earth's surface has fallen so much that the air near the surface is cooler than that above—that is, there is a state of temperature inversion. Under these conditions fallout reaches a maximum which is further modified by the presence or absence of upward currents—that is, the greatest fallout is with the least upward current. These conditions have two corollaries. The first is that early morning should be the most trying time for asthmatics and sufferers from hay fever, and the second is that the perpetual activity of a city should have a profound effect upon fallout.

The first corollary is demonstrably true, and the second has been investigated by H. A. Heise and E. R. Heise,[1] both by making aeroplane counts and by building a model city. The aeroplane counts were carried out during a temperature inversion, and although the country particle counts were high, the city particle counts were low and decreased from windward to leeward. The model city was warmed to a temperature greater than that of the surrounding air (as is the situation with real cities), and it was shown that *Lycopodium* spores did not settle on it. Heise and Heise comment that this phenomenon should hold true for radioactive fallout, and that a great degree of protection may be afforded by ensuring that a city is at all times warmer than the surrounding countryside, provided, of course, that the city receives no direct hit. The cinema exodus from the cities to the good earth, in a time of stress, may prove to be a Scylla and Charybdis situation.

CARCINOMA OF THE THYROID IN CHILDREN.

ONE of the topics of the moment is radiation hazard. An important aspect of this problem is that of medical irradiation and in particular irradiation involving the thyroid gland. It has always been one of the theoretical disadvantages, if not more, of radioiodine therapy in thyroid disease that a carcinoma may be induced in thyroid tissue. Pari-passu information on the effects of any sort of irradiation upon the body is required. Within

[1] *J.A.M.A.*, March 9, 1957.

recent months a great deal of information has been accumulated which is highly suggestive, without being conclusive.

There have been several reports of thyroid carcinomata in children who have previously received irradiation, usually, to the thymus gland. For instance, D. E. Clark[1] reports that of 15 children with thyroid carcinoma who were seen by him, all had previously received irradiation which could have involved the thyroid. George H. Fetterman[2] reports ten cases of carcinoma of the thyroid in children under the age of sixteen years who have attended the Children's Hospital in Pittsburgh. From 1926 to 1950 there was only one patient with a carcinoma of the thyroid out of a total attendance of 88,392. In the five years from 1951 to 1955 seven more patients were seen out of a total attendance of 29,461. In addition to this Fetterman reexamined all the histological material from all the surgical operations known to involve the thyroid in the years 1926 to 1955; but no further cases were discovered. In this same period only four cases of benign nodular or adenomatous thyroid enlargement were seen. The only two cases from neighbouring hospitals have been included in Fetterman's study, making a total of ten cases. Of the ten children concerned eight had received prior irradiation. The reasons for irradiation were: thymus gland enlargement in three cases, hæmangiomata in two, enlarged lymph nodes in two, and enlarged tonsils in one. The average latent period was 7·6 years.

Various criticisms have been made of the suggested relationship between thyroid carcinoma and irradiation. Of the total number in the published figures about 50% of the subjects of juvenile thyroid carcinoma have received irradiation. The two commonest reasons for irradiation have been enlarged lymph nodes and thymic enlargement. It has been suggested that the lymph gland enlargement has been a manifestation of metastases from a thyroid carcinoma with the primary tumour becoming obvious at a later date. Secondly, it has been suggested that there may be a relationship between thyroid carcinoma and thymic enlargement. As with a thyroid carcinoma and irradiation relationship, the two latter suggestions remain to be proved. The answer may merely be that thyroid carcinoma in children is becoming more common as the result of an unknown carcinogenesis.

ANOTHER NEUROLEPTIC DRUG.

WHEN Harry Beckman wrote his introduction to the 1956-1957 "Year Book of Drug Therapy", he referred somewhat feelingly to "the recent great upsurge of interest in drugs that affect mood and behavior", and stated that research in this field had recently assumed "an urgent and most unbecomingly hectic character". It will be readily conceded that these drugs have become a prominent medical fashion at the present time; but this is not entirely a bad thing. In spite of the disadvantages that can accompany their abuse, their introduction has brought a new era into the treatment of mental disorders, and investigation must go on. This being so, interest attaches to a clinical trial carried out by J. Delay, P. Pichot and R. Ropert[3] on the acid maleate of ethylone-3-dimethylamino-3'-propyl-10-phenothiazine (1522 C.B.). In their introductory remarks, they state that since the discovery of the particular action of chlorpromazine in mental disorders, an important development has taken place in psychiatric therapy, comparable in its effects with that brought about twenty years ago by the introduction of shock treatment. The unique action of the new chemotherapeutic substances that have been studied during the last five years has necessitated the creation of a new term, "neuroleptics". Delay and his co-workers state that 1522 C.B. is closely allied to chlorpromazine chemically. It is put up in four forms: ampoules for intramuscular injection (10 milligrammes), ampoules for intravenous injection (25 milligrammes), tablets (10 milligrammes), drops (one-tenth of a milligramme). They have used only the first three forms; the drops are too weak for psychiatric use. They have studied its effects on 31 patients who had psychiatric disorders, chiefly psychoses, and present the results of their investigation. They state that experimentally the properties of 1522 C.B., in particular its action on the central nervous system, are similar to those of chlorpromazine, but greater. Clinical trials have shown that the drug has a field of activity that compares favourably with that of other such drugs already known, especially chlorpromazine. Its action in states of excitement, more particularly maniacal syndromes, is good enough for it to be included in the group of drugs covered by the term "neuroleptics". Its action in chronic psychoses, although no final assessment can yet be made, seems comparable with that of the other neuroleptics. The authors state that their clinical investigation did not reveal any new indication for its use, in comparison with the drugs that have already been studied; on the contrary, it simply confirmed the existing limitations, more especially in depressed states. Delay and his co-workers used 1522 C.B. in the treatment of patients in hospital as well as for maintenance therapy. An interesting observation made was that when the drug was given by intramuscular injection, it was extremely well tolerated locally. In their series they encountered no complication affecting the blood, the skin or the liver. They state categorically that the efficacy of the drug is superior to that of chlorpromazine in equal dosage.

[1] *J.A.M.A.*, November 5, 1955.
[2] *Am. J. Dis. Child.*, December, 1956.
[3] *Presse méd.*, March 16, 1957.

OPERATIVE INJURY OF THE URETER.

MOST surgeons operating in the abdomen and pelvis have been concerned at one time or another about the safety of the ureter. The difficult hysterectomy, excision of widespread cancer, and operations for unusual appendiceal lesions and atypical pancreatic and mesenteric abnormalities are causes of concern in this regard, and there may be problems associated with direct inguinal hernia repair. In a paper on the management of the injured ureter, Vincent O'Conor[1] refers to an increase in frequency of ureteric damage during the past ten or fifteen years. Among associated conditions, in addition to those mentioned above, he lists perforation of the ureter during cystoscopic procedures, for example, manipulation of a catheter past a calculus, and the necrosing effect of irradiation after therapy. He states that the most favourable time for repair of the lesion is at the time of accident or operation. For this reason it is imperative to recognize the mishap as soon as possible. The longer the situation exists unrecognized, the greater is the difficulty of correction and the more serious are the effects. The theme of the paper is that pre-operative assessment of the ureteric position should be attempted whenever it is suspected that trouble may be encountered, and that, if necessary, introduction of ureteral catheters should be used to aid identification during difficult dissections. Cooperation between urologist and surgeon is to be more readily sought in such cases. Even if such catheters are not recognized *in situ* during dissection, injury to the ureter will readily reveal the catheter.

There should be no need to comment that the surgeon must have a complete knowledge of the development, anatomy and anomalies of the ureter. Identification of the ureter is vitally important (i) where it crosses the bifurcation of the iliac vessels, (ii) in the ovarian fossæ, and (iii) where it passes behind the uterine artery. With dissection deep in the pelvis, the surgeon at all times has in mind the position of the bladder wall and the intravesical course of the ureter. It is an interesting fact that many injuries of the ureter, resulting from the placing of clamps or ligatures, are stated to have occurred when dissection was apparently easy. This recalls a similar claim made about injuries of the common bile duct. In both cases there is no doubt that immediate recognition and repair of such damage give the patient the best opportunity of surviving without complication.

[1] *J.A.M.A.*, November 24, 1956.

When accidental ligation is recognized during operation, release of the tie, with or without the passage of a ureteral catheter, will usually suffice. If the ureter has actually been cut, the ends must be identified, and over a catheter, direct end-to-end anastomosis should be performed. Chromicized catgut (4/0) on an atraumatic needle is recommended, with two or three mattress sutures. Protection against extravasation of urine is an indication for drainage of the local area. Should the situation contraindicate a prolonged search for the site of injury, or if repair is too difficult, nephrostomy should be performed after the abdominal wound has been closed, again with provision for adequate drainage. The complete simple ligation of the ureter, known to be followed frequently by asymptomatic renal atrophy, is too easy a way out of the difficulty of unilateral ureteral injury. Unless previous renal functional tests have demonstrated normal kidney function on the unaffected side, the patient may not survive. And even if a normal kidney is present on the other side, loss of function of one kidney is not to be lightly produced.

If oliguria or anuria develops during the first hours after an operation in which the ureter may have been a proximal relation, the possibility of ligature or an injury to the ureter should be entertained. Reexploration of the abdominal wound, examination of the suspect ureter and the cooperation of the urologist by insertion of a ureteral catheter will occasionally become necessary. The aid of the latter may save the patient and surgeon a prolonged search for areas of ligation or injury in œdematous tissues without finding the cause. Suture of the sectioned ureter may be necessary. If the injury has been low in the pelvis, within three to five centimetres of the bladder, reimplantation of the proximal portion should be performed into the bladder, either by the pull-through-and-suture technique or by the mucosa-to-mucosa elliptical anastomosis of Nesbit. On occasion, implantation of the lower half of a ureter has been effected into the sigmoid colon or opposite ureter.

THE JUBILEE OF "THE QUARTERLY JOURNAL OF MEDICINE".

ONE of our most distinguished contemporaries, *The Quarterly Journal of Medicine*, is this year celebrating its jubilee. This journal, like a number of other good things in medicine, owes its origin primarily to William Osler. Apparently the notion of a new journal, which ultimately became *The Quarterly Journal of Medicine*, began in the last decade of the nineteenth century, when A. A. Kanthack, A. E. Garrod and W. Hale-White met together in order to find a means of issuing a medical journal "which would publish papers that were hardly likely to appeal to the mass of the profession, but which ought to be published, as being concerned with the advancement of medical science". However, Kanthack died in 1898, and the idea remained in abeyance until Osler visited Oxford in 1904. In the journal's special jubilee issue, Sir Russell Brain describes an important meeting in May, 1906, which was attended by Osler, Garrod, Hale-White, Rose Bradford, Rolleston and Hutchison. Osler agreed to help in starting a magazine such as they had in mind, and suggested the Clarendon Press as publishers. He also suggested the formation of a national association of physicians, somewhat on the lines of the Association of American Physicians, which both would be a pleasant gathering and also would form the nucleus of a public for the magazine. The association became the Association of Physicians of Great Britain and Ireland. The journal, after negotiation with various people, made its appearance in 1907, and has continued to our day. It seems that the journal was first described as the *Archives of Medicine*, but this was soon changed to *The Quarterly Journal of Medicine*, for some reason that today is not clear. Osler himself was editor of the journal for twelve years, and he has been described as "indefatigable in encouraging its growth, shaping its policies and smoothing out its difficulties". The list of those who have served as editors in the subsequent years contains many distinguished names, but is too long to quote here. *The Quarterly Journal of Medicine* has achieved an enviable status in the medical world, and we join with many others in offering congratulations on fifty years of service to medicine.

STRANGE AIR-BORNE PARTICLES.

ONE would imagine that the last place to find reports of unidentified objects would be a journal of industrial medicine, whose contributors would be well acquainted with the industrial maladies of a saggar maker's bottom knocker. However, Albert F. Bush, the Associate Professor of Engineering in the University of California, and his co-workers[1] have encountered some particles which to them are completely unknown. They publish some electron micrographs of air samples, and invite comment upon them, and wonder if they can be identified. The unknown particles are mainly needles and flakes which have been caught during air pollution research. The needles are of the general configuration and size of a virus.

SELECTION OF PERSONNEL FOR SPACE FLIGHT.

The Journal of Aviation Medicine has recently[2] published an article on the selection of crews for space ships. There has, of course, been a great deal written on this subject within recent years; much of what has been written seems pointless, and the proposed tests seem useless. This may seem a bold statement, but it can be supported by a great weight of evidence. Space flight, in which a handful of men will be cooped up together for long periods of time with no privacy, is one of the limbs of human endeavour which touches the fanatical. As such it must be grouped with the activities of mountaineers, Antarctic explorers, rowing crews and military leaders. A swift count of these groups in the past, if it had been made, would have revealed so many goats that no action would have been possible. Admittedly there are countless examples of misfits in the list given, but surely the point is that man with all his talents cannot predict heroes (particularly the cynic's hero), at least not yet.

PHOTOSENSITIVE CHLORPROMAZINE DERMATITIS.

THAT widely used drug chlorpromazine, which has in many ways been introduced into general usage too quickly, has many side effects. There have been scattered reports in the literature of photosensitivity reactions, but these have not been straightforward, in that they have not occurred consistently in any one person. M. M. Cahn and E. J. Levy[3] have investigated this problem. They studied five patients who had developed sunlight-induced erythemato-papular eruptions with pruritus whilst receiving chlorpromazine. In addition they studied five volunteers who were used as controls. All ten patients were exposed to ultra-violet light from a quartz-mercury arc source, but no eruptions were evolved. Further inquiry into the histories of the five photosensitive patients revealed that the eruptions had occurred only on days of intense sunlight when the atmosphere was relatively free from smoke and dust. This would suggest that the precipitating cause is ultra-violet activity of a wave-length other than that of the mercury lamp, and probably of the order of less than 3000 Å. It is interesting to find that the eruptions were apparently induced by only a small band of ultra-violet activity. This is of value in the unravelling of dermatological ætiology, and is also of value in that chlorpromazine photosensitivity does not necessarily involve withdrawal of the drug. Whether this would hold true for the intense sunlight of an Australian summer remains to be seen.

[1] *Arch. Indust. Health*, January, 1957.
[2] *J. Aviation Med.*, February, 1957.
[3] *Arch. Dermat.*, January, 1957.

Abstracts from Medical Literature.

GYNÆCOLOGY AND OBSTETRICS.

Breech Presentation.

J. E. HALL AND S. KOHL (*Am. J. Obst. & Gynec.*, November, 1956) report a survey of 1456 breech presentations among 43,513 deliveries at seven American institutions during the five-year period 1950 to 1954. All babies weighed over 999 grammes. The incidence of breech presentation in this series was 3·4%. The serious problem of prematurity complicating breech presentation is emphasized by a 30·5% incidence in comparison with a prematurity incidence of 10·3% in cases other than breech presentation. The most frequent type of breech presentation was the frank breech, followed by footling, then complete breech. There was very little difference in perinatal loss among the three types of breech presentation. This series confirms the observation that breech presentation is more common in *multiparæ*. Hydramnios was present in 1·5% of all these breech cases, an incidence three times as great as normal and possibly explained by the high incidence of fœtal malformation in the series (7·9%). The average duration of labour was nine hours for *primiparæ* and six hours for *multiparæ*, indicating that breech presentation does not prolong labour in the majority of cases. No analgesia was given in 35% of the breech labours and 213 patients of the series were delivered without anæsthesia. Complications of labour included prolapse of cord (72 cases), accidental hæmorrhage (50 cases), secondary uterine inertia (46 cases), retained placenta (42 cases) and post-partum shock (36 cases). Delivery was accomplished by some form of extraction in 71% of the cases. Cæsarean section accounted for 10·7% of all the breech deliveries, resulting in a fœtal survival of 90·4%. Excluding deaths prior to the onset of labour, the fœtal loss of mature infants delivered by section was 1·6%. An increased perinatal loss was noted in patients who received "Pitocin" stimulation with breech presentation. There was no perinatal mortality among primigravid patients over thirty-five years of age treated by Cæsarean section. The perinatal loss in mature infants was three times greater if the interval between rupture of the membranes and delivery exceeded twenty-four hours. The most frequent cause of perinatal death was some type of respiratory disturbance, understandable with the high incidence of prematurity. The second most common finding was cerebral hæmorrhage. There were three maternal deaths in the series, an incidence of 0·2%. The authors advise an X-ray examination of the fœtus and X-ray pelvimetry in all breech presentations, minimal analgesia during labour, interference when necessary during delivery under inhalation anæsthesia, and forceps application to the after-coming head if there is any delay in its delivery. Cæsarean section is recommended as the method of delivery in the following cases: contracted or borderline pelvis, large infants, bad obstetrical history, *primigravidæ* over thirty-five years of age, most cases of uterine inertia, *placenta prævia* and selected cases of accidental hæmorrhage and prolapse of the umbilical cord.

Fibrinogen-Fibrin Conversion Syndrome.

C. P. HODGKINSON (*West. J. Surg.*, December, 1956) discusses certain hæmorrhagic and embolic manifestations found in diseases such as *abruptio placentæ*, long intrauterine retention of a dead fœtus, amniotic fluid embolism *et cetera*. He states that the accepted theory in this syndrome is that hyperthromboplastinæmia causes changes in the blood-clotting mechanism in two directions: occlusion of terminal arterioles with insoluble fibrin results in shock, while depletion of fibrinogen accounts for hæmorrhage. The physiology of thromboplastin, fibrinogen and fibrin is briefly described. The fibrinogen-fibrin syndrome is said to have a dual pathological possibility—embolism producing shock if the process is sudden and severe, hæmorrhage of uncoagulable blood when the process is less acute and plasma fibrinogen is gradually depleted. In clinical practice cell injury of some types is a common cause of the initial thromboplastinæmia. Accordingly the syndrome may occur in the crush syndrome, surgical trauma, hæmolytic blood reaction, fœtal autolysis *et cetera*. Amniotic fluid embolism characterized by sudden shock, and usually death, is thought to be due to the intravenous infusion of thromboplastin-containing fluid. In *abruptio placentæ* the onset is less acute and hæmorrhage of uncoagulable blood predominates over shock from arteriolar embolism by insoluble fibrin gel. Long intrauterine retention of a dead fœtus is associated with a latent hypofibrinogenæmia resulting in hæmorrhage. Necrosis of the renal cortex, pituitary and adrenals is considered a variant of the fibrinogen-fibrin syndrome. Observation of the "clot observation test" (Weiner, Reid and Roby) is of practical value in confirming the diagnosis of this syndrome. Clinical recognition of the disease is not difficult; the main diagnostic features are shock with associated symptoms or hæmorrhage of uncoagulable blood either alone or intermixed. The author outlines principles of treatment for *abruptio placentæ* and for the "dead fœtus syndrome". A warning is given that fibrinogen, though readily available for intravenous infusion, is not without the risk of giving the patient infective hepatitis.

Prolapse of the Umbilical Cord.

W. G. SLADE AND J. H. RANDALL (*Am. J. Obst. & Gynec.*, November, 1956) report a study of 63 cases of prolapse of the umbilical cord among 15,578 deliveries at the University of Iowa Hospital (1940 to 1953). A survey of 24 different publications reporting 4296 cases of prolapsed cord gave an incidence of one case in 156 deliveries. Maladaptation of the presenting part through contracted pelvis, pelvic tumour or obstetrical manipulation disposes towards cord prolapse. In this series there was an incidence of 4·8% of contracted pelves with prolapse of the cord. The risk of cord prolapse in contracted pelvis should be anticipated by performing a careful pelvic examination following rupture of the membranes. The authors found prolapse of the cord most commonly in transverse or shoulder presentations, next in breech presentations, and least often in vertex presentations. There was a gross fœtal mortality rate of 42·8% in the series, mainly caused by delay in diagnosis of prolapse of the cord, a high operative delivery rate, and an increased incidence of prematurity. There was a 28·6% incidence of prematurity among these patients. The authors found the risk of prolapse nearly twice as great in *multiparæ* as in *primiparæ*; it was prone to occur with nearly equal frequency at all degrees of dilatation of the cervix. Multiple pregnancy carried a greater risk of prolapse of the cord on account of the increased incidence of prematurity, increased incidence of hydramnios and the high presenting part of the second twin. The fœtal mortality risk was more than twice as great when the presenting part was not engaged, and the degree of dilatation of the cervix at the time of diagnosis had a direct bearing on the fœtal mortality rate. There was a progressive increase in fœtal deaths with increase of time between diagnosis of cord prolapse and delivery of the baby. Operative delivery of patients in this series by forceps, breech extraction or Cæsarean section was at a rate of 30% to 40%. The perinatal mortality rate was 55·5% for premature infants and 37·7% for mature babies. The stillbirth rate was 33%, fifteen times as great as the stillbirth rate for all deliveries. There was one maternal death in the series due to severe sepsis, and the risks of post-partum hæmorrhage and morbid puerperium were quadrupled. The authors emphasize the importance of early diagnosis and prompt treatment. Frequent and repeated checks of the fœtal heart beat and a routine vaginal examination soon after rupture of the membranes are considered valuable aids in early diagnosis. They recommend the following steps in treatment for prolapse of the cord with a viable baby: immediate postural treatment should be carried out; the presenting part should be held up by an assistant with a finger in the vagina until delivery is accomplished; the baby is delivered as quickly as possible, by the vaginal route if conditions are suitable, otherwise by Cæsarean section.

Hæmostatic Defects in Pregnancy.

J. A. PRITCHARD (*Am. J. Obst. & Gynec.*, November,. 1956) discusses the common clinical conditions in obstetrics which may result in hæmorrhage due to interference with the blood coagulation mechanism. These conditions are: severe *abruptio placentæ*, amniotic fluid embolism or prolonged intrauterine retention of a dead fœtus. The author draws attention to two other causes of hæmorrhage due to disorders of the hæmostatic mechanism of the blood, namely the transfusion of incompatible blood and infected abortion. A study was made of 22 patients with intrauterine death of the fœtus at sixteen or more weeks' gestation, and retention of the fœtus *in utero* for five or more weeks, and it was found that six had

clinically significant hypofibrinogenæmia. Hypofibrinogenæmia in these patients develops slowly over a period of days or weeks. The demonstration of a normal clotting time for whole blood or a normal plasma prothrombin activity does not rule out the possibility of clinically significant hypofibrinogenæmia. The author considers that spontaneous labour or labour induced and maintained with "Pitocin" does not cause a significant change in the level of circulating fibrinogen, even when there is preexisting hypofibrinogenæmia. Patients with hypofibrinogenæmia associated with prolonged intrauterine retention of a dead fœtus show a rapid increase in the amount of circulating fibrinogen following delivery of the products of conception. This observation is thought to support the theory that hypofibrinogenæmia in this syndrome results, not from decreased production, but from increased utilization of fibrinogen which ceases as soon as delivery is effected. Severe hæmorrhage has been known to occur from hypofibrinogenæmia and thrombocytopenia caused by the transfusion of incompatible blood. The author reports a patient who was mistakenly given "A" group blood instead of "O" group for hæmorrhage associated with a miscarriage at three months' gestation. A severe transfusion reaction was followed by bleeding from the nose, mouth and vagina. The intravenous infusion of three grammes of fibrinogen resulted in prompt cessation of bleeding and a normal plasma fibrinogen concentration. A case of infected abortion with serious disorders of the blood coagulating mechanism and massive hæmolysis due to *Clostridium perfringens* septicæmia is reported. Bleeding occurred from all needle puncture sites, ecchymoses were evident in the abdominal wall, and a large hæmatoma developed beneath the oxygen mask. The author considers that the hæmostatic defect in this case may occur in a similar manner to that produced by the transfusion of incompatible blood or may be due to extensive liver damage.

Experience with Pregnancy in the Bicornuate Uterus.

F. H. FALLS (*Am. J. Obst. & Gynec.*, December, 1956) reviews his experience with pregnancy in the bicornuate uterus. All uteri at some stage of their development are bicornuate, and one or both horns may fail to develop. Failure of fusion produces a series of anomalies with *uterus didelphus* at one end and *uterus arcuatus* at the other, and the frequency of their appearance varies directly as they approach the arcuate uterus. When pregnancy occurs in the bicornuate uterus a disproportionate number of complications of pregnancy and labour occurs. The diagnosis is relatively easy with cases of gross abnormality such as septate vagina, twin cervices *et cetera*, but in cases of *uterus septus* or *subseptus* diagnosis is difficult without uterine exploration. Habitual abortion at the third to the fifth month suggests, among other causes, the possibility of a bicornuate uterus. These uteri are generally more irritable and the placenta is frequently heart-shaped or bipartite. The author suggests that in addition to embryological maldevelopment there are also possibly circulatory and nervous abnormalities. Premature labour is also common in this type of uterus. Intrauterine fœtal hypoxia as shown by abnormalities in the fœtal heart sounds is frequently caused by abnormalities in placentation and uterine circulation. Intrauterine fœtal death can occur for no other valid reason. Breech presentation is much more common and occasionally is obliquely transverse with greater tendency to cord prolapse. After the sixth month transverse or obliquely transverse lies are common. External version is usually impossible in a septate or subseptate uterus. Face or brow presentation and *opisthotonos fœtus* are often associated with a bicornuate uterus. Premature detachment of the placenta is also more common. Prolapse of the cord occurs frequently for various reasons, and in the third stage eversion of the uterus, atonic post-partum hæmorrhage due to the inert type of labour, and retained placenta can occur. Septa in the vagina may have to be cut to ensure delivery in the second stage. Repeated abortions in a septate uterus may require treatment by hysterotomy with removal of the septum.

Spinal Anæsthesia in More than Thirty-Four Thousand Vaginal Deliveries.

G. A. MACER (*West. J. Surg.*, December, 1956) reports results of spinal anæsthesia (single dose) in 34,936 vaginal deliveries. Various adverse criticisms of spinal anæsthesia in obstetrics are mentioned, and mortality rates due to inhalation anæsthesia are given. The patients reported were all delivered vaginally and had the spinal anæsthetic given by the *accoucheur*, either specialist obstetrician or general practitioner. The incidence of spinal anæsthesia at the two hospitals concerned was 69%, and had increased to over 80% in 1954. The author considers that the administrator of spinal anæsthesia should be well trained and adhere to a proven technique. The author's technique, using a hyperbaric solution of 5·0 to 6·0 milligrammes of tetracaine U.S.P. in 2·0 cubic centimetres of 10% glucose solution is detailed. The anæsthetic is usually given within an hour of expected delivery and the level of anæsthesia is controlled by tilting the table. There were no maternal deaths from anæsthesia in this series, no serious neurological complications, no infections around the site of injection, and no case of purulent meningitis. Adverse effects reported by Macer were: hypotension, headaches and meningismus. There were less than six cases of severe hypotension in the series, and the condition responded to treatment when recognized promptly. Headaches are an annoying complication in 10% to 18% of patients. Their incidence and severity have been reduced by improvements in technique. Symptomatic treatment with bed rest is the only treatment necessary in most cases. Meningismus is thought to be caused by intradural extravasation of blood and is characterized by nuchal spasm and headaches. The author does not consider spinal anæsthesia to be the perfect anæsthetic for childbirth, but it is the most satisfactory one available. A properly given spinal anæsthetic is not considered more hazardous than inhalation anæsthesia. No increase in the incidence of post-partum hæmorrhage or retained placenta was observed with spinal anæsthesia. The fœtus is said to be better oxygenated and rarely requires resuscitation, and spinal anæsthesia is considered advantageous for the premature infant.

Intestinal Obstruction Following Pelvic Surgery for Benign Disease.

F. S. BOYNTON AND R. W. BONSNES (*Am. J. Obst. & Gynec.*, January, 1957) review 30 cases of intestinal obstruction following 3217 abdominal operations over a five-year period at the New York Hospital Women's Clinic. Of these cases 12 were diagnosed as mechanical obstruction and 18 as adynamic ileus, an incidence of 0·4 and 0·6 *per centum* respectively. Hysterectomy and myomectomy were the most common operations, but both mechanical obstructions and ileus occurred after other types of pelvic surgery. The commonest indication for the operation was the presence of fibromyomata. The treatment for mechanical obstruction was operative in eight, intubation in four, with parenteral maintenance in all cases; there was one death in this group. Of the four patients treated conservatively, thr e recovered and one died. The management of the group with ileus consisted of intubation with parenteral fluid maintenance until bowel sounds returned. Analysis of the management of the patients who developed ileus showed that the critical time was before the development of the classical signs and symptoms, and closer attention should be given during the immediate post-operative period to those patients who fail to progress normally with respect to oral intake.

The Stein-Leventhal Syndrome and Associated Endometrial Carcinoma.

R. L. JACKSON AND M. B. DOCKERTY (*Am. J. Obst. & Gynec.*, January, 1957) have studied the clinical and pathological data on 43 patients who had the Stein-Leventhal syndrome. The majority of these patients were obese, excessively hairy, hypertensive and infertile. There was a high incidence of amenorrhœa. The characteristic ovarian changes of bilateral enlargement, thick cortical rinds and polycystic cortices were present. In uncomplicated cases surgical wedge resection of the ovaries was curative. Sixteen of the 43 patients had associated endometrial carcinoma and the authors consider that this association is not coincidental. The ages in the neoplastic group ranged from twenty-eight to forty-eight years, with the majority of patients in their late thirties and forties. In 14 of this group abnormal bleeding was present. In view of the fact that 20% of women under forty years of age with endometrial carcinoma gave evidence of the Stein-Leventhal syndrome, it might be well to follow closely all patients on whom the wedge operation has been performed to ascertain whether the carcinogenic tendency has been prevented. Patients suffering from the syndrome should undergo a dilatation and curettage prior to definitive surgical attack on the ovaries.

Medical Societies.

MEDICAL DEFENCE SOCIETY OF QUEENSLAND.

ANNUAL MEETING.

THE fifty-fifth annual meeting of the Medical Defence Society of Queensland was held at British Medical Association House, 88 L'Estrange Terrace, Kelvin Grove, Brisbane, on Wednesday, March 27, 1957, at 5 p.m.

Annual Report.

The annual report for the year ended December 31, 1956, was adopted. The report is as follows:

The Council of the Medical Defence Society of Queensland has pleasure in presenting the fifty-fifth annual report for the year ended December 31, 1956.

Membership.

The membership of the Society is now 811 as against 741 last year. During the year 96 new members were elected and seven returned from overseas. Our losses were as follows: left the State 19, resignation 1, lapsed by arrears 10, deceased 3.[a]

There are 20 members who have indemnity insurance cover with other approved organizations.

Obituary.

We regret to record the deaths of the following members: Dr. Harold R. Love, Dr. E. T. C. Schmidt and Dr. J. W. Heaslop.

Office-Bearers and Council, 1956.

The following office-bearers were elected by Council: *President*, Dr. Neville G. Sutton; *Vice-President*, Dr. G. W. Macartney; *Honorary Treasurer*, Dr. T. V. Stubbs Brown; *Honorary Secretary*, Dr. F. W. R. Lukin; *Councillors for 1956*, Dr. T. R. Biggs, Dr. H. W. Horn, Dr. Athol Quayle, Dr. W. J. Saxton, Dr. F. Garrett Scoles, Dr. J. G. Wagner.

The following councillors, who retired in conformity with the by-laws, were unanimously reelected: Dr. H. W. Horn, Dr. Athol Quayle and Dr. T. R. Biggs. Dr. Horn has been on leave during his trip overseas.

Medico-Legal.

During the year, five cases were submitted to the Society for advice or action, and four were carried over from the previous year. All were dealt with to the satisfaction of the Society and of the members concerned. Of the four cases carried over from last year, two were settled and two are still pending. Writs have been issued in three of the other cases which the Society is defending. Other matters on which members sought advice were dealt with by Council or by the secretariat.

General.

In view of the opinion expressed at the last annual meeting, that it is considered all indemnity insurance of members of the Medical Defence Society of Queensland should be effected through the affiliation scheme with the Medical Protection Society, Limited, London, and not by any other "approved organization" as provided for in Article 21A, it was decided that legal advice be obtained concerning the altering of the Articles of Association of the Queensland Society in this regard.

In reply to an inquiry, the London Society advised that graduates with "limited registration" are admitted to membership on the understanding that they are covered only in respect of their approved hospital appointments. Should any provisionally registered practitioner undertake professional work outside the scope of his limited registration, it would be deemed to be unregistered practice, and therefore the Society would not cover a member in this respect.

This information was promulgated to the profession by the Queensland Branch of the British Medical Association at the request of the Council of the Medical Defence Society of Queensland.

During his visit overseas, the President, Dr. Neville G. Sutton, had an opportunity of meeting officers of the Medical Protection Society, Limited, London. Information was received concerning the impact of national insurance on medical defence and on other matters of mutual interest.

Owing to the removal of the Queensland Branch of the British Medical Association to new premises situated at 88 L'Estrange Terrace, Kelvin Grove, Brisbane, the office of the Medical Defence Society of Queensland will be changing its address early in 1957.

Finance.

It will be shown by the balance sheet that the net surplus for the year ended December 31, 1956, amounted to £764 7s. 7d.

Some items of income and expenditure are as follows:

	£	s.	d.
Receipts:			
Annual Subscriptions, Medical Defence Society of Queensland	632	7	0
Entrance Fees	92	8	0
Subscriptions, Indemnity Insurance, Medical Protection Society, Limited, London	5,141	16	3
Interest—			
Commonwealth Government Inscribed Stock	303	7	5
Commonwealth Savings Bank Interest	2	15	11
Expenditure:			
Amount remitted to Medical Protection Society	3,786	3	11
Secretarial and Clerical Assistance	256	0	0
Rent	5	0	0
Postages, Duty Stamps, Bank Charges, Printing and Stationery	21	15	6
Audit Fee	16	16	0
Federal Income tax for year ended December 31, 1955	21	4	0

The total assets of the Society amount to £11,811 8s. 6d.

An amount of £8663 3s. is invested in Commonwealth Government Inscribed Stock.

NEVILLE G. SUTTON,
President.

Balance Sheet.

The balance sheet for the year ended December 31, 1956, was adopted.

Election of Councillors and Auditors.

The following councillors, who had retired in conformity with the by-laws of the Society, were unanimously reelected: Dr. Neville G. Sutton, Dr. F. W. R. Lukin, Dr. F. Garrett Scoles. Dr. B. N. Adsett was elected to fill a vacancy on the Council.

Messrs. R. G. Groom and Company, Limited, Chartered Accountants (Australia), were elected auditors for the ensuing year.

Appreciation to Mrs. Myra Spooner.

It was resolved that the meeting record its great indebtedness to Mrs. Myra Spooner, who has held the position of Secretary of the Society for many years.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

RETURN OF THE MEDICAL ESTABLISHMENT: A LIST OF THE MEDICAL GENTLEMEN IN THE COLONY OF NEW SOUTH WALES WITH THE RESPECTIVE STATIONS WHERE THEY ARE DOING DUTY.[1]

[From "Historical Records of Australia", Volume VI.]

Thos Jamison Esqr—Principal Surgeon Sydney.

Mr. Jas Thompson—First assistant on leave of absence. Mr. Chas Throsby doing his duty at Kingston Hunter's River a distant Settlement.

Mr. D. Wentworth—Second Assistant at Parramatta.

Mr. Jas Mileham—Third Assistant at do.

Mr. John Savage—Fourth Assistant, in Europe under Sentence of a Court Martial.[2]

[1] From the original in the Mitchell Library, Sydney.

[2] John Savage had been sentenced by court martial to be cashiered, the charge being that he had declined to attend a woman in difficult labour. The sentence was however not confirmed as that was considered not to be a military offence.

Mr. Jacob Mountgamer—Acting Assistant Surgeon, Port Dalrympe.

Mr. Jas Luttrell—do., Sydney.

Mr. Conolan (Connellan)—do., Norfolk Island.

Mr. Thos Arndell—Acting Assistant Surgeon, Hawkesbury a Settlement which extends seventy miles on the Banks of the River.

Being a stranger to the intensions of His Majestys Ministers I most humbly beg leave to observe that my motives for making the present representations are that no blame may be attached to me hereafter, and here I have to remark that Five of the Medical Gentlemen now doing duty in this Colony and its Dependencies are only acting: should they resign their Colonial Appointments and retire, as they have not been Confirmed what will be the Situation of those Settlements where they are doing duty: exclusive of this evil there are Settlements at this moment destitute of a Resident Assistant Surgeon: in our former letter I have only wrote for Six additional Assistants and they would have more patients to attend to than any other description of Surgeons in His Majesty's Service either by Sea or Land; after this official Communication I trust no reprehensibility will be attached to him who has the Honor to be with greatest respect &c.

THOS JAMISON, Principal Surgeon.

Sydney Oct 20th 1806.

Special Correspondence.

LONDON LETTER.

BY OUR SPECIAL CORRESPONDENT.

Research on Rheumatism.

IN a letter to *The Times*, Lord Astor of Hever appealed for funds to further the work of the Empire Rheumatism Council, the money to be spent on fundamental research on rheumatism by providing research fellowships, scholarships, university teaching posts in rheumatology, improved laboratory facilities and the extension of specialized hospital centres. An increase in the activities of the mobile field unit for investigating the prevalence of rheumatism among people working and living in different environments, in particular industries and communities, is also projected.

The appeal target of £250,000 is trifling compared to the huge sums spent annually in Great Britain on the medical treatment and social care of rheumatic sufferers. Rheumatic disorders are responsible for more economic loss than any other single bodily disorder, and for nearly one-tenth of the incapacity of the working population and of lost working days. The loss in output cannot be less than £80,000,000 a year.

Remedial services are everywhere insufficient, and often only palliative. Merely to expand existing services would be less rewarding in the long run than to provide more facilities for research into the causes of rheumatism, which would lead to earlier treatment and the possibility of prevention. At the present time there are ten centres in England and Wales for teaching and research, five in London hospitals and five provincial, including Bath and Harrogate. Perhaps the most outstanding example of the neglect of existing opportunities for the study of rheumatism is the present situation of the Royal National Hospital for Rheumatic Diseases at Bath. This hospital was founded over 200 years ago, and prior to the last war it was planned to demolish it and build a new hospital. Funds were raised and the foundation stone was about to be laid by the late Queen Mary, but the war intervened. The old hospital suffered damage by bombs, but it has carried on, although obsolete and dilapidated. In 1948, under the *National Health Service Act*, the hospital was taken over by the State, and the voluntary funds were appropriated. Many attempts have been made since to secure a new building, but last year the State finally decided not to provide a new hospital. The hospital authorities are again pressing the Ministry of Health for funds to repair and renovate the old building thoroughly, and there is strong support, both local and national, from all interested in rheumatic disorders and in the care of the rheumatic sufferer.

General Practitioner Training Scheme.

The aims of the scheme are to provide a system of training new entrants to general practice, to enable them to obtain first-hand experience expertly supervised in an exacting branch of the profession, and to expand their outlook from hospital to domiciliary practice. The scheme has now been in operation seven years and has been subject to two reviews. The number of doctors appointed to train has fallen since the beginning of the scheme, and over recent years has averaged 200. The latest report of the sub-committee appointed by the General Medical Services Committee to review the training scheme has concluded that the scheme fully justified itself and should remain a permanent feature of the National Health Service. Two major complaints of the scheme have been examined—that is, the lack of uniformity in the selection of trainers and the abuse of the scheme. Appointments as trainers are primarily teaching appointments, and are not to be used as a means of relieving hardship among elderly or infirm practitioners, or as a means of providing a doctor with an assistant where it would not be economic to employ him. Selection of trainers is made by local medical committees, who should be fully alive to their responsibilities. Not only must the applicant's professional skill and teaching ability be of a high standard, but his practice commitments should be taken into account—that is, where the burden of his professional work is too onerous to permit him to undertake training. Age and health are also factors. Further, the trainee should not be used as a *locum tenens*—that is, take charge of a practice when his trainer is ill or on holiday. Twelve months' training is regarded as the right period. The committee regard the present training grant of £150 as no more than adequate to recompense the principal for the additional work and responsibility.

Medical Records.

The accumulation of hospital records presents a problem which has to be faced sooner or later by most hospitals. Records are bulky, and the space required for their storage is often needed to house new departments. Hospital records contain information of historical and clinical interest, and their preservation is valuable to present and future historians, both lay and medical. Some hospitals employ records officers, among whose duties is the preservation of documents of potential interest. Two London hospitals, Saint Bartholomew's and Saint Thomas's, whose records go back to the sixteenth century, have professional archivists. The records of these ancient foundations bring to light, besides items of medical interest, interesting features of the social and economic life of the times. Under the National Health Service, hospital records became public records, and rules for their disposal have recently been issued under the *Public Records Office Act*. The main object of these instructions is the preservation of any documents which are, or may in future become, of historical interest. In the case of medical records, the rules authorize the destruction of certain classes of medical documents—case records, X-ray films *et cetera*—after a stated period of years. The question of what to keep and what to destroy has always been a difficult one, and these new rules for the guidance of hospital authorities are timely.

Hospital Call System.

Most hospitals require some system for locating the various members of the staff within its walls, especially those peripatetic members of the medical staff, the resident medical officers. Various systems are used—loud speakers, bells, buzzers and coloured lights. Bells, buzzers and coloured lights work on a code applicable to a particular individual. All these systems have disadvantages, their effectiveness is limited to the places where they are installed, and their noise is disturbing to patients and staff. In a large hospital, owing to the number of people who may be called, the codes become too long and complicated. At Saint Thomas's Hospital, London, much work has been done to evolve an ideal call system, one which would enable any individual to be called without any other person being disturbed, and which would also ensure that the recipient would be positively attracted to his call. This necessitates an audible signal rather than visual, but one which could be heard only by the person required. This in turn requires each recipient to carry an individual receiver, capable of converting an inaudible signal (a wireless wave) into an audible one. After considerable research and development, a very satisfactory magnetic calling system for medical staff has been devised and installed.

The hospital buildings are surrounded by a loop of wire attached to a transmitter powered by the mains. Signals are sent out on individual frequencies to selected recipients within the hospital. The individual receivers are of pocket size, not much bigger than a fountain pen, and are carried by the medical staff. The way this system operates is for the ward requiring the doctor to telephone the request to the porter's lodge. The porter operates the appropriate switch, and the recipient, on hearing the call (a persistent buzz), goes to the nearest telephone and inquires for the message. It is possible by using a modified receiver to transmit speech, but even in its simplest form it has given complete satisfaction.

Radiation Hazards.

Last year the Minister of Health announced in Parliament his intention to set up a committee to review the present practice of radiology in relation to the hazards to man from nuclear and allied radiation. This committee has now been set up and begun its work under the chairmanship of Lord Adrian, O.M., F.R.S., M.D., F.R.C.P., Master of Trinity College, Cambridge.

A limited survey by the Medical Research Council has suggested that X rays and radiation from radioactive isotopes used for medical diagnosis and treatment are the most important source of man-made radiation to which the population is exposed. The task of the committee is to widen the inquiry and make recommendations concerning the use of diagnostic X rays and radiotherapy for non-malignant conditions.

Tuberculosis in Glasgow.

The industrial areas of Scotland have an unenviable reputation in the high incidence and death rate from tuberculosis. A major attack on the disease is being made in Glasgow by the Department of Health for Scotland, the Regional Hospital Boards and the Glasgow Health and Welfare Department. This campaign, backed by inspired publicity, has already achieved remarkable success. Interest and enthusiasm have been aroused by publicity methods which are usually associated with North America. An Auster aircraft has flown over the city, employing what the experts call "a sky shouting" technique. Popular football teams, such as the Rangers and Celtic, have attended the clinics, as well as every stage and dance band personality within range. Prizes, such as a car, washing machine, refrigerator *et cetera*, have been offered to those who have passed through the clinics. Yellow lapel badges are given to each person, which also entitle him to more modest prizes. The original supply of these badges (250,000) has been exhausted. The campaign has been aided by the general strike of shipyard workers with time on their hands. Although the campaign has run only half its course, 400,000 persons have been radiologically examined in the 36 clinics, and this figure may eventually reach 700,000. Glasgow's population of persons over the age of fourteen is 780,000. So far, the survey has identified two cases of the disease in every 1000 persons examined. Provision has been made for immediate admission to hospital and the thousand beds available are regarded as adequate.

Correspondence.

BURROUGHS WELLCOME FELLOWSHIP.

SIR: Burroughs Wellcome and Company (Australia), Limited, has founded an annual research Fellowship as from 1957, to be held by a research worker in the Diabetic and Metabolic Unit of Alfred Hospital.

The Fellowship (for 1957) has been awarded to Mr. Peter R. Davoren, B.Sc. Mr. Davoren graduated in 1952, when he was awarded the exhibition in biochemistry. Since that time he has worked on the purification and characterization of a peptidase from kidney tissue. Following this, he has spent three years working with Dr. J. Bornstein on the action of glucagon on the isolated perfused rat's liver. This work has served to establish a technique for the provision of a respiring tissue for detailed biochemical investigation of the metabolism of such tissues. This work has been undertaken in fulfilment of the requirements for the degree of doctor of philosophy in the University of Melbourne.

As Burroughs Wellcome Fellow, Mr. Davoren proposes to develop a technique for the perfusion of the isolated cat's pancreas, by which he hopes to study the control of insulin synthesis using radiochemical techniques.

I should be pleased if the foundation and award of this Fellowship could receive some publicity in your journal.

Yours, etc.,

C. G. RANKIN, Manager.

Alfred Hospital,
Prahran,
Victoria.
May 10, 1957.

"FLUOTHANE": AUSTRALIA: TRADE MARK 2540.

SIR: May we draw attention to a small point on page 325 of your issue dated March 9, 1957, in your article entitled "Fluorthane".

Actually this trade mark name is "Fluothane", and you may care to put this on record for future reference, especially as the writer of the article appears to have been under the genuine misunderstanding that "Fluorthane" is the proper spelling.

May we add that we much appreciate your comments on this new anæsthetic.

Yours, etc.,

L. J. HOOLEY (Division Trade Marks Section), Imperial Chemical Industries, Limited (Pharmaceuticals Division).

Fulshaw Hall,
Wilmslow,
Cheshire,
England.
May 10, 1957.

THE MEDICAL PROFESSION AND THE PLIGHT OF ABORIGINES

SIR: The recent outcry in the Press, and other vehicles of popular expression, about the medical care of the coloured people of Australia, with the accompanying condemnation of State Governments, calls for some comment. A letter on this subject (M. J. AUSTRALIA, May 11, 1957) will serve as further ammunition for the opportunist critics of this country in the General Assembly of the United Nations.

The real facts are somewhat different. The majority of the coloured people in Australia have access to the same medical treatment as does the rest of the population. In New South Wales, Victoria and the settled areas of the other States this condition applies. In remote districts of Queensland, Western Australia, South Australia and the Northern Territory, mission stations and Government settlements provide medical centres, from which patients can be sent to hospital in case of necessity.

In Queensland there are now no tribal natives who cannot make contact with mission stations where their children are cared for.

In the far north, centred on Thursday Island, is a network of radio stations. A medical service, analogous to the Royal Flying Doctor Service, has functioned for the past twenty years.

The scourges of yaws, hookworm and malaria are controlled by mission workers, who have been trained in the use of various drugs. Even the great killer, tuberculosis, is now being successfully overcome. In all, about 10,000 coloured people are covered by this organization.

It would be more appropriate if certain church leaders and others would give words of praise to workers like the Reverend Bill Mackenzie and his wife, who have given more than thirty years' devoted service to the coloured people of Aurukun in the Cape York Peninsula. Instead, they rather seek to achieve notoriety for themselves by their ill-informed outbursts.

There remain the natives of the Centre. These people are living as their ancestors did, hunting scarce game and gathering roots of plants. They will gradually be attracted to the more adequate European diet. Many of them prefer the old life, with its incredible hardship and semi-starvation.

The fashionable belief that the early settlers of this country went about killing off the natives is a gross libel of the finest section of our pioneers. There were some isolated incidents, but they were as nothing compared with intertribal and intratribal killings. I recall that my own mother, in our primitive homestead in North Queensland,

sat calmly in a room with her six young children, while a yelling mob of armed natives came searching for one of their young women, who had broken some tribal law, and who had fled to the white man for protection. My father faced the angry tribe and was forced to fire a few shots to get rid of them.

Finally, the impact of European disease, particularly tuberculosis, should be remembered as the first cause in the diminution of the native population.

Yours, etc.,

J. R. NIMMO.

Duntroon,
May 17, 1957.

STREPTOCOCCAL PROPHYLAXIS IN RHEUMATIC FEVER AND CHOREA.

SIR: In a recent number of THE MEDICAL JOURNAL OF AUSTRALIA, interesting articles appeared on rheumatic infections, and advice was given on the methods of preventing recurrences by the regular and prolonged administration of sulphonamides or oral penicillin. The report from the Institute of Child Health stated that there was no evidence to show that the removal of tonsils prevented recurrences of rheumatic fever.

Few general practitioners attend large numbers of patients suffering from this disease, but we do live amongst our patients, and have opportunities of observing them throughout the years. Therefore I think that our observations should be considered as having some bearing on this subject of the prophylaxis of rheumatic fever.

I have been in practice in the one town for twenty-nine years, and during that time have attended about three or four cases of rheumatic fever annually. Practically all patients commenced the illness with tonsillitis, and all had their tonsils removed either during the convalescent stage or soon afterwards. I have watched many of these children grow to adult life, and have not seen one case of a recurrence of the disease. Until the last three years we had no other method of prophylaxis, but now I am using the sulphonamides or oral penicillin as well. However, especially in the country, it is very difficult to be sure that the tablets are given regularly.

It would be interesting to have the views of general practitioners on this important subject.

Yours, etc.,

ELLEN M. KENT HUGHES, M.B., B.S.

141 Faulkner Street,
Armidale,
New South Wales.
May 17, 1957.

Medical Practice.

POLICE OFFENCES (AMENDMENT) ACT, 1908, AS AMENDED, OF NEW SOUTH WALES.

PROCLAMATION.

I, SIR JOHN NORTHCOTT, Knight Commander of the Most Distinguished Order of Saint Michael and Saint George, Knight Commander of the Royal Victorian Order, Companion of the Most Honourable Order of the Bath, Lieutenant-General on the Retired List of the Australian Military Forces, Governor of the State of New South Wales and its Dependencies in the Commonwealth of Australia, with the advice of the Executive Council, do, by this my Proclamation, declare that Part VI of the Police Offences (Amendment) Act, 1908, as amended, shall apply to:

(i) Diethylthiambutene (3 - diethylamino - 1, 1 - di - (2' - Thienyl)-1-butene), its salts and any preparation, admixture, extract or other substance containing not less than one-fifth per centum of diethylthiambutene;

(ii) 1, 3 - dimethyl - 4 - phenyl - 4 - propionoxyhexamethyleneimine, its salts and any preparation, admixture, extract or other substance containing not less than one-fifth per centum of 1,3-dimethyl-4-phenyl-4-propionoxyhexamethyleneimine;

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED MAY 11, 1957.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	2	3(2)	3(1)	..	..	..	..	..	8
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	2(1)	10(10)	2(2)	..	..	..	1	..	15
Diphtheria	3	4(4)	3	..	2(2)	6	..	..	18
Dysentery (Bacillary)	..	2(2)	..	5(5)	1(1)	..	..	..	8
Encephalitis	2	2(2)	..	..	..	..	..	..	4
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	60(20)	15(2)	..	2(2)	2	6(2)	1	..	86
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	2	..	..	..	..	..	2
Malaria	..	..	1	..	..	3	..	..	4
Meningococcal Infection	1	1(1)	..	..	..	2	..	..	4
Ophthalmia	..	..	..	..	2	..	..	..	2
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	1(1)	..	..	1	..	..	..	..	2
Puerperal Fever	1(1)	1	..	..	..	..	..	..	2
Rubella	..	23(16)	..	13(3)	3(1)	..	..	..	39
Salmonella Infection	..	..	..	1(1)	..	..	..	..	1
Scarlet Fever	12(1)	10(6)	1(1)	10(6)	3(3)	..	..	..	36
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	5	..	..	..	5
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	26(10)	12(11)	3(1)	4(4)	6(6)	2	1	..	54
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

(iii) 3-hydroxy-N-phenethylmorphinan, its salts and any preparation, admixture, extract or other substance containing not less than one-fifth per centum of 3-hydroxy-N-phenethylmorphinan;

(iv) 4-morpholino-2,2-diphenylethylbutyrate, its salts and any preparation, admixture, extract or other substance containing not less than one-fifth per centum of 4-morpholino-2,2-diphenylethylbutyrate;

in the same manner as it applies to the drugs mentioned in paragraph (a) of subsection (2) of section 18 of the said Act.

Signed and Sealed at Sydney this eighth day of May one thousand nine hundred and fifty-seven.

By His Excellency's Command.

C. A. KELLY.

GOD SAVE THE QUEEN!

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Revision Course at Rachel Forster Hospital for Women and Children.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a full-time revision course will be held from Monday to Friday, July 29 to August 2, 1957, at the Rachel Forster Hospital for Women and Children, Redfern. The course is open to all members of the medical profession, and limited accommodation is available for women graduates at £3 13s. 6d. The programme is as follows:

Monday, July 29: 9.45 a.m., opening of revision course; 10.15 a.m., "Investigation and Treatment of Leucorrhœa", Dr. Gwen Gerrard; 11.30 a.m., demonstration of pre-operative gynæcological cases, Dr. Gwen Gerrard; 2 p.m., clinical demonstration of medical cases with emphasis on treatment (cases will include (*a*) arthritic, (*b*) gastro-intestinal, (*c*) cardiac disorders), Dr. Willa Nelson, Dr. Clare Weekes, Dr. Pat Manuel, Dr. Gwynneth Roberts, Dr. Nanette De Coek.

Tuesday, July 30: 9.30 a.m., presentation of pædiatric cases, Dr. G. Geikie and Dr. E. Miller; 11 a.m., "Recent Advances in the Treatment of Thyroid Dysfunction", Dr. Helen Taylor; 11.45 a.m., (*a*) "Some Associations Between E.N.T. and Dental Disease", (*b*) "The Husky Voice", Dr. Brenda Laws; 2 p.m., demonstration of gastroscopy, Dr. A. Middleton; 3.30 p.m., surgical panel—open question time, Dr. A. Middleton and Dr. R. Hudson.

Wednesday, July 31: 9.30 a.m., "Diagnosis and Treatment of Common Skin Disorders", Dr. Jean Mason-Johnson; 10.15 a.m., "Anticipation of Difficulties in Anæsthesia", Dr. Gwen Bernard; 11.15 a.m., "Otitis Media in Children", Dr. Patricia Davey; 12.15 p.m., "Causes and Treatment of Frequency in Women", Dr. Colin Edwards. Free afternoon.

Thursday, August 1: 9.30 a.m., demonstration of surgical cases, Dr. Margery Scott-Young; 10.45 a.m., discussion on the best way to use the services of the pathologist, Dr. M. Drury-White; 11.45 a.m., "Investigation of Sterility", Dr. Lois Benson; 2 p.m., demonstration of carcinoma and other breast conditions, Dr. Kathleen Cuningham; 4 p.m., "Modern Uses and Complications of Blood Transfusion", Dr. R. J. Walsh (Director, New South Wales Red Cross Blood Transfusion Service).

Friday, August 2: 9.30 a.m., "Recent Advances in Psychiatric Therapy", Dr. Joan Fotheringham; 10.45 a.m., (*a*) "Headache of Ocular Origin", Dr. E. Wilson; (*b*) "Diagnosis and Treatment of Eye Conditions Commonly Seen in General Practice", Dr. E. Fisher; 11.45 a.m., "The Reticuloses (Hodgkin's Disease, Leuchæmia and Lymphosarcoma)", Dr. Reginald Walker; 2 p.m., demonstration of X-ray films and discussion on uses and limitations of radiography, Dr. Marjorie Dalgarno and Dr. Jean Edwards; 3 p.m., "Minor Orthopædic Disabilities", Dr. Denis Rowe.

The fee for attendance is £5 5s., and written application, enclosing remittance, and indicating whether accommodation is required, should be made to the Course Secretary, Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney, not later than July 5, 1957. Telephones: BU 4497-8. Telegraphic address: "Postgrad Sydney."

Medical Appointments.

Professor Edward Ford has been appointed a member of the Board of Health, New South Wales.

Dr. N. R. Wyndham has been appointed a Director on the Board of the Prince Henry Hospital, Sydney, on the nomination of the Royal Australasian College of Surgeons.

Deaths.

THE following deaths have been announced:

MCCLEMENS.—Dorothy Mary McClemens, on April 15, 1957, at Bellevue Hill, New South Wales.

STONE.—Grace Clara Stone, on May 10, 1957, at Melbourne.

LONGMORE.—Philip James Longmore, on May 12, 1957, at Melbourne.

JOHNSTON.—George Arthur William Johnston, on May 19, 1957, at Sydney.

Diary for the Month.

JUNE 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
JUNE 5.—Western Australian Branch, B.M.A.: Branch Council.
JUNE 5.—Victorian Branch, B.M.A.: Clinical Meeting.
JUNE 6.—South Australian Branch, B.M.A.: Council Meeting.
JUNE 7.—Queensland Branch, B.M.A.: General Meeting.
JUNE 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JUNE 14.—Tasmanian Branch, B.M.A.: Branch Council.
JUNE 14.—Queensland Branch, B.M.A.: Council Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Queensland Branch (Honorary Secretary, B.M.A. House, 88 L'Estrange Terrace, Kelvin Grove, Brisbane): Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £5 *per annum* within Australia and the British Commonwealth of Nations, and £6 *per annum* within America and foreign countries, payable in advance.